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Protocol

Development of an Ex Vivo Model Simulating the Human Urethra: Application to Drug Diffusion

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Abstract

The development of topically applied drugs for the human urethra requires experimental models that simulate the urethra's structural characteristics and assess drug diffusion through its various tissue layers. This study aimed to describe a novel ex vivo model that simulates the different layers of the male urethral wall and to evaluate its applicability for investigating drug diffusion using a halofuginone (HF)-containing intraurethral gel as a model formulation, to support the future development of intraurethral therapies. The study used the human ureter as a substitute for the urethra because both tissues share a similar histological structure and the ureter is more readily available. The experimental model consisted of two parts. The first part employed a diffusion cell to investigate the diffusion kinetics of three HF gel formulations over a period of 2 hours. The second part used the formulation selected from the first phase to evaluate the three-dimensional (3D) distribution of HF following ex vivo intraurethral instillation. Three gel formulations with different viscosities were prepared. A high-performance liquid chromatography (HPLC) method was used to determine the concentration of HF diffused into the human ureteral wall. Following ex vivo intraurethral instillation, HF was uniformly distributed throughout the tissue. No HF was detected in the receiver compartment during the 2-hour diffusion period. These findings suggest that topical delivery of HF via an intraurethral gel may be a promising therapeutic approach for treating and preventing urethral stricture recurrence. The development and characterization of this ex vivo urethral model may facilitate the evaluation and development of new intraurethral therapies for urethral diseases.

Keywords: Ex vivo model, urethra, ureter, halofuginone gel, wall diffusion

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1. Introduction

Urethral stricture is a common urological disease with an incidence of up to 0.3% in adult males and can seriously impair patients' quality of life [1]. It is a fibrotic disorder characterized by the deposition of noncompliant scar tissue within the urethral wall, leading to a reduction in the urethral lumen diameter [2].

Halofuginone (HF), a synthetic derivative of a quinazolinone alkaloid isolated from Dichroa febrifuga, has attracted considerable interest because of its potent antifibrotic properties. It has demonstrated therapeutic potential in preventing urethral stricture formation and recurrence in animal models [3, 4]. Since the pathological process primarily develops within the inner layers of the urethral wall, effective treatment requires adequate penetration and retention of the drug within these tissues following local administration.

However, the development of topical intraurethral therapies remains limited by the lack of appropriate preclinical models for evaluating drug diffusion and tissue distribution of the drug in human urethral tissue. Most previous studies have been conducted using animal models, ex vivo tissues, organ-on-chip technologies, and micro-physiological systems that do not accurately reproduce the anatomical and histological characteristics of the human tissue and do not fully replicate the 3D architecture and extracellular matrix of native human organs. To address some of these limitations, we have developed a simplified ex vivo model for studying drug bioavailability in the human urethra. This experimental model uses the human ureter as a substitute for the human urethra due to their comparable histological architecture. Furthermore, human ureters are easier to obtain than human urethral tissue, making them a practical alternative for ex vivo studies. The objective of the present study was to describe a novel ex vivo model that simulates the different layers of the male urethral wall and to evaluate its applicability for investigating drug diffusion using an intraurethral HF-containing gel as a model formulation. This model is intended to support the future development and preclinical evaluation of topical intraurethral therapies.

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Overview of the procedure

In this protocol, we provide detailed instructions for the model and how the model can be used to study the diffusion of HF through the wall of the human urethra.

The procedure is summarized in Fig.1. It can be divided into two phases. The first phase involves studying the vertical diffusion of the drug through the diffusion cell using the portion of the human urethra. This phase allows the study of diffusion kinetics of drugs after two hours. This phase was developed during the Preliminary study. The second phase consists of studying the 3D diffusion of the drug by reproducing the physiological condition of the human urethra.

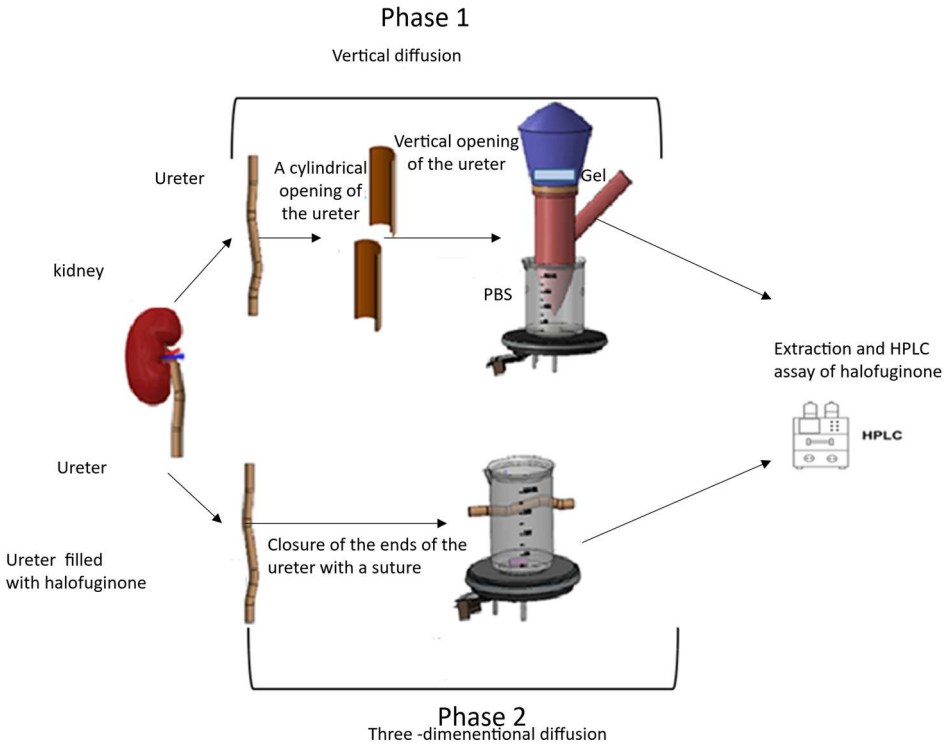

Fig. 1. Diffusion study of drugs using urethral model

The model consists of two complementary experimental approaches. **(Phase1)** Vertical diffusion study using a diffusion cell system. The human ureter tissue segment is positioned between the donor and receptor compartments, with the hydrogel formulation applied to the luminal side of the tissue. The receptor chamber contains phosphate-buffered saline (PBS) as the receiving medium and is maintained under controlled conditions to quantify drug diffusion across the tissue barrier. **(Phase 2)** Three-dimensional (3D) diffusion study using a segment of human ureter in its tubular form. The hydrogel formulation is introduced into the ureteral lumen, and both extremities of the tissue segment are sealed to maintain contact between the formulation and the tissue wall. The sealed ureter is then incubated in PBS at 37°C. The concentration of halofuginone in the human ureter tissue and in the PBS was quantified using high-performance liquid chromatography (HPLC).

Advantages and limitations of the approach

Our model offers a simple and reproducible approach for studying drug diffusion through the human urethral wall and evaluating the tissue bioavailability of topically administered formulations intended for the treatment of urethral conditions. To the best of our knowledge, no physiologically relevant ex vivo human urethral model has been described to date. Most studies on the urethral administration of drugs have relied on in vivo animal models, particularly rabbits, due to their anatomical similarities to the human urethra [3]. However, interspecies differences remain a major limitation when it comes to predicting how a drug will behave in human tissues. Furthermore, recent advances in human tissue-based preclinical models—including ex vivo tissues, “organ-on-chip” technologies, microphysiological systems, and advanced diffusion platforms—have significantly improved the evaluation of drug delivery systems. These engineered platforms allow for dynamic control of the tissue microenvironment through fluid flow, mechanical stimulation, and multicellular interactions. However, they generally rely on reconstituted tissues and cannot fully replicate the 3D architecture and extracellular matrix of native human organs. This new model overcomes this limitation by using a freshly harvested human ureter as the donor tissue. The human ureter and urethra share several structural characteristics, including a urothelial mucosa, a layer of smooth muscle, and an outer layer of connective tissue (adventitia), and both originate from similar embryonic tissues [5,6]. These common characteristics constitute comparable biological barriers that influence the penetration, distribution, and retention of locally administered compounds. The main advantages of this model are its simplicity, reproducibility, and the preservation of the native histological architecture of human tissues.

These characteristics make it suitable for evaluating both the diffusion kinetics of drugs and their spatial distribution within tissues. It therefore serves as a valuable complement to conventional in vitro assays and as an intermediate step before animal or clinical studies, thereby reducing uncertainties associated with interspecies extrapolation. Despite these advantages, several limitations should be acknowledged. First, although the ureter closely resembles the urethra, it does not fully replicate the natural urethral environment. Compared to the urethra, the ureter has a thinner muscle layer, different biomechanical properties related to ureteral peristalsis, and subtle differences in the organization of the extracellular matrix—all of which are factors that may influence tissue permeability and drug transport. Second, as with any ex vivo model, vascular perfusion, urine flow, immune responses, and active cellular metabolism are absent, which limits the assessment to passive drug diffusion and tissue retention rather than the complete pharmacokinetic behavior observed in vivo. Practical constraints must also be taken into account. The availability of fresh human ureters depends on kidney transplant programs and obtaining the appropriate ethical approvals; furthermore, the length of the excess ureter varies from one donor to another, which may limit the amount of tissue available for experimentation. Furthermore, inter-donor variability—including differences in age, tissue composition, extracellular matrix organization, and intrinsic permeability—may contribute to variability in drug diffusion and must be taken into account when interpreting the results.

Finally, tissue viability was not directly assessed in this study. Although all samples were collected immediately after kidney removal, stored under standardized conditions, and processed within a few hours to minimize tissue deterioration, no metabolic, histological, or viability tests were performed. Consequently, the maintenance of cell viability throughout the experiments cannot be formally confirmed. Nevertheless, since the primary objective of this study was to investigate short-term passive diffusion, the preservation of tissue architecture was considered the most critical requirement. Future studies incorporating quantitative viability assessments would further strengthen the biological characterization. Future studies incorporating quantitative viability assessments would further strengthen the biological characterization and translational relevance of this ex vivo model.

2. Protocol

Application of method and target audience

The histological similarity between ureteral tissue and the human urethra offers an interesting opportunity for investigating treatments for pathologies of the human urinary tract. The development of this model would make it possible to evaluate both the diffusion kinetics of drugs and their spatial distribution in tissues before clinical trials. This model can be used as an in vitro platform to evaluate new therapies for urethral diseases. It overcomes the ethical and practical limitations associated with the use of human urethral tissue, as, from both ethical and feasibility perspectives, it is not possible to use the human urethra for the development of new drugs. In fact, we used this model to study the diffusion kinetics of an intraurethral gel releasing HF for the treatment of urethral stricture. The gel formulation selected was the same as that used in our previous study [7]. This model can also be used to characterize several topical drugs designed for urethral pathologies. Indeed, our model allows the development and characterization of an alprostadil-based intraurethral gel for the treatment of erectile dysfunction. This gel may be more effective than current treatments and may avoid the side effects associated with systemic drug absorption. The proposed model may provide a valuable tool for the development and evaluation of intraurethral drug delivery systems. Future studies are needed to determine its suitability for specific therapeutic applications. This model is suitable for use by researchers in urology, andrology, oncology, infectiology, and sexology involved in the development of new therapeutic formulations.

Comparison with other methods

Several studies have been conducted using other biomaterials, such as xenogeneic acellular tissue matrices [8,9] and synthetic polymers [10,11], to replace urological tissues when they are no longer available. The standard animal model used for urethral reconstruction is the New Zealand rabbit [10,12–14]. Two studies have been conducted using a dog model [15,16], two others used human cadaveric tissues [17,18], and another study used a pig model [19]. The use of the ureter as a model is valuable for pharmacological studies. This model has several advantages over other models, including the preservation of histological architecture and tubular geometry of the human urethra, providing a platform for diffusion studies.

Experimental design

The main procedure describes how to establish our simplified model and its use to study the diffusion kinetics of HF.

Samples

Sixteen human ureters were provided by the Department of Urology at Sahloul University Hospital in Sousse following kidney transplantation. All available donors capable of providing an adequate ureteral segment were included in the study. The ureteral samples were recovered after donor approval and stored in the organ preservation solution Euro-Collins®. This solution allows tissue preservation for up to 48 hours under standardized conditions.

However, to minimize potential tissue deterioration, all samples were used within the first few hours following ureter procurement. The samples consisted of tubular ureteral segments, with lengths varying according to the anatomical requirements of the kidney recipient. Only ureteral segments providing a sufficient length of at least 3 cm were included to allow the completion of the experimental procedures. The ureters were immersed in physiological saline solution to remove residual preservation solution and then gently dried using Whatman filter paper (Fig. 2).

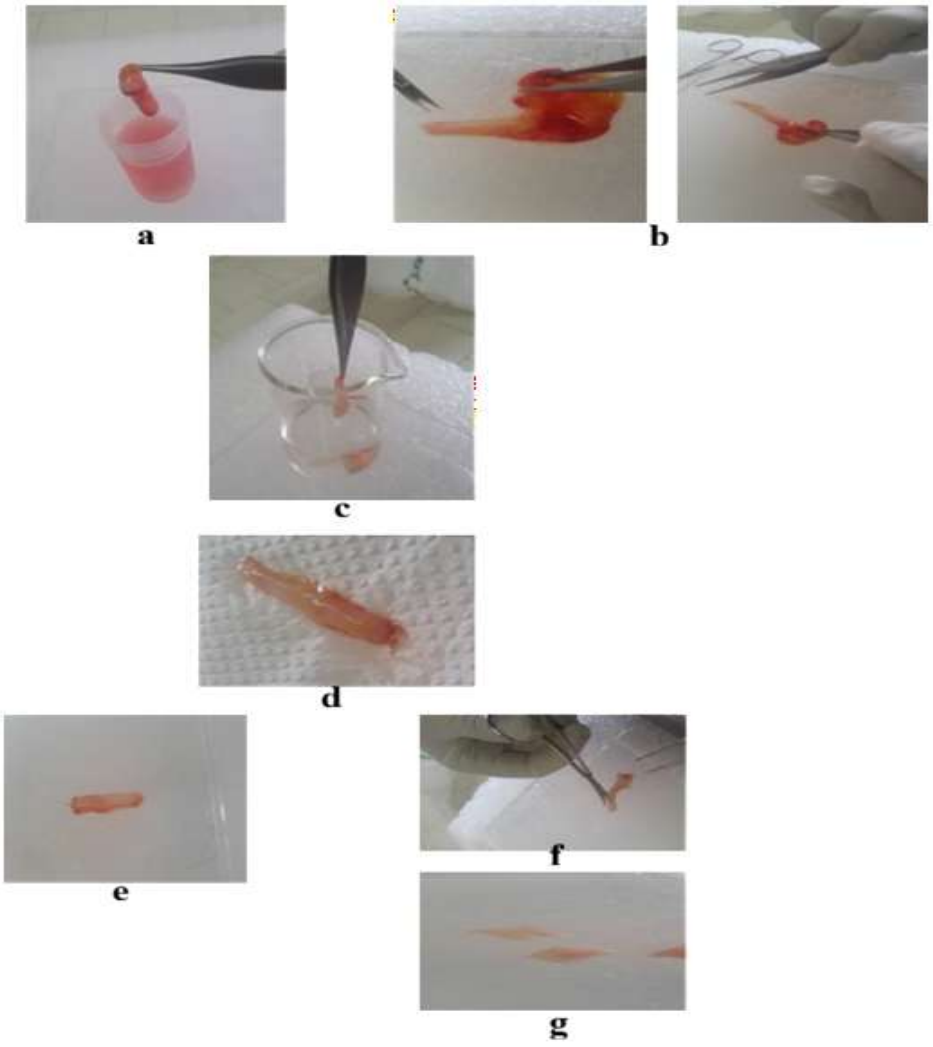

Fig.2. Preparation of human ureter samples.

(a) Receipt of ureter specimens and preservation in Eurocollins® solution; (b) removal of surrounding adipose tissue; (c) washing of the ureter with physiological saline solution; (d) drying of the ureter surface; (e) maintenance of the ureter in its tubular configuration; (f) longitudinal opening of the ureter; and (g) sectioning of the ureter into rectangular segments.

Model description

In this section, we describe a novel ex vivo model based on freshly excised human ureter for investigating the diffusion kinetics of locally administered drugs and their penetration into tissue as a surrogate for the human urethral wall. Two experiments were carried out using this organ.

We first conducted an experiment to study ex vivo permeability and ureteral retention. In this experiment, we placed a uniform 50 mm² section of the ureteral wall into a diffusion cell (Fig. 1 phase1). During two hours of exposure to the gel, the exposed ureteral areas were removed from the diffusion cell at predetermined intervals, and the ureter fragments were rinsed with physiological saline solution to remove excess drug.

The amount of drug retained in each ureter section and in PBS solution was measured by the HPLC method validated in our previous study after a liquid-liquid extraction step using isopropanol [20].

The two-hour exposure period was chosen based on the observation that, as the bladder fills, the urge to urinate gradually intensifies, and that intraurethral administration of the gel can further accentuate this sensation [21]. For this reason, a two-hour incubation period was selected as a physiologically appropriate compromise, providing sufficient time for the drug to diffuse while remaining consistent with the normal physiology of the lower urinary tract. The kinetic profile of diffusion through the wall allows us to compare different formulations under identical and uniform conditions.

The second experiment evaluated the three-dimensional distribution of HF using fresh human ureter segments (approximately 3 cm long) to replicate the natural tubular geometry of the urethra (Fig. 1 phase 2). During this experiment, the HF-based gel was instilled into the ureter, which was then immersed in PBS for 2 hours. The ureter was then cut into equal sections. Subsequently, the retention of

the active substance within each portion of the ureteral wall and the amount of HF diffused into the PBS were quantified by HPLC [20].

3. Materials

Biological materials

Fresh human ureter segments were harvested from tissue that is typically discarded during kidney transplants, after obtaining written informed consent from all donors. The use of these samples for research purposes was approved by the Research Ethics Committee of Sahloul University Hospital in Tunisia (ref. no. 13218), and all procedures were conducted in accordance with the principles of the Declaration of Helsinki.

Reagents

Halofuginone hydrobromide (HF) standard was obtained from Discovery Fine Chemicals (Dorset, United Kingdom), and imipramine hydrochloride (internal standard) was purchased from Sigma Ultra (England). Ammonium sulfate was supplied by Riedel-de Haën. HPLC-grade acetonitrile was obtained from Lab-Scan (Supergradient grade). Ammonium acetate, anhydrous sodium carbonate, trypsin, ethyl acetate, and carboxymethyl sodium cellulose were purchased from Sigma-Aldrich. Sodium hydroxide, dichloromethane, and triethylamine were obtained from Fluka. Acetic acid (85%) was purchased from Merck (Germany), and isopropanol was supplied by Lab-Scan. Phosphate-buffered saline (PBS) and Euro-Collins® organ preservation solution were also used throughout the study.

Purified water was produced using a Millipore purification system (Arium 611DI/611UV). All chemicals and solvents were of analytical or HPLC grade.

Equipments

Chromatographic analyses were performed using an Agilent 1200 HPLC system equipped with a G1311A quaternary pump, G1322A vacuum degasser, G1315D diode array detector, thermostated column compartment, and a manual injector (5 µL injection volume). Separation was achieved at 30°C using a Lichrospher® C18 analytical column (250 × 4 mm, 5 µm particle size) coupled to a Lichrospher® 100 RP18 guard column (4 × 4 mm, 5 µm particle size). A custom-designed diffusion cell was used for ex vivo diffusion studies. Additional equipment included a propeller agitator (Heidolph RZR2041), a viscometer (Labomat Essor), a precision balance (Adventurer, OHAUS), a vortex mixer (Bioblock Maxi Mix 2, Code 92622), a pH meter (Hanna Instruments), a centrifuge (HPW Instruments), a rotary evaporator (Rotavapor RE200), an Intelli-Mixer RM-2L agitator, and a FALC hot plate.

4. Procedure

Preparation of human ureters for ex vivo application (Fig.2)

Human ureter sample preparation involved several successive steps. Upon receipt, the human ureters were stored in Euro-Collins® preservation solution until use. The surrounding adipose tissue was carefully removed using scissors, after which the ureter was opened longitudinally to obtain a rectangular tissue sample. The samples were then immersed in physiological saline solution to remove any traces of the preservation solution, followed by washing with phosphate-buffered saline (PBS).

After removal from the PBS solution, the samples were dried using Whatman No. 1 filter paper. Finally, the integrity of the ureteral tissue was verified before use to ensure the suitability of the samples for the experiments.

Ex vivo retention and release study (Fig.1 phase 1)

Each gel formulation was evaluated in five independent experiments using ureter specimens obtained from five different donors (n = 5 biological replicates per formulation). Before each experiment, the modified diffusion cells were cleaned with PBS solution. The receiver compartment was then filled with 2.5 mL of PBS (pH 7.4), and a small magnetic stir bar was placed inside to maintain constant stirring at 100 rpm.

The ureter samples were positioned between the donor and receiver compartments of the diffusion cells, which were maintained at 37 ± 1 °C throughout the experiment. The donor compartment was filled with 300 mg of HF-containing gel and sealed with Parafilm® to prevent gel evaporation. Aliquots of 100 µL were collected from the receiver compartment at predetermined time intervals and replaced with an equal volume of fresh PBS.

At the end of each exposure period (0, 30, 60, 90, and 120 min), the corresponding ureter fragment was collected. Excess gel was removed using a sterile compress, after which each ureter section was rinsed twice with physiological saline solution for 5 minutes and subsequently washed twice with PBS for 5 minutes before further analysis.

Spatial distribution of drugs within the ureteral wall (Fig.1 phase 2)

Fresh human ureter, measuring at least 3 cm in length, was used in the study of the 3D distribution of drugs. The ureteral segment was rinsed twice with physiological saline solution for 5 minutes and then washed twice with PBS for 5 minutes. One end of the segment was hermetically sealed with sutures before the HF gel was introduced into the lumen using a syringe. After instillation, the other end of the ureter was also hermetically sealed with sutures. The ureteral segment was then placed in a test tube containing PBS maintained at 37 °C. After the incubation period, both ends of the ureter were removed, and the excess gel was eliminated using a sterile compress. The ureter was then opened longitudinally, fixed flat on a working surface, and cut transversely and longitudinally with a scalpel to obtain a minimum of eight equal portions, each with a surface area of 37 mm². Finally, each section was rinsed twice with physiological saline solution for 5 minutes and washed twice with PBS for 5 minutes before subsequent analysis.

Extraction of HF

Each human ureter portion was placed into a 2-ml Eppendorf tube, and 1 mL of 10% (w/v) sodium carbonate solution (pH 8.0) was added. The tissue was manually homogenized using scissors, after which 100 µL of the internal standard (IS, imipramine; 0.1 mg/mL) and HF were

added to the homogenate. The homogenate was incubated with 1 mg of trypsin in a water bath at 37 °C to perform enzymatic hydrolysis. The resulting mixture was then transferred into a 15-mL centrifuge tube, and proteins were precipitated by adding 600 mg of ammonium sulfate. The sample was mixed on a vortex mixer for 1 minute, followed by the addition of 4 mL of propan-2-ol.

The mixture was homogenized by agitation and centrifuged at 4000 rpm. A 2-mL aliquot of the supernatant was transferred into a clean tube and evaporated to dryness at 55 °C under reduced pressure using a rotary evaporator. Finally, the residue was reconstituted in 100 µL of the mobile phase.

Chromatographic studies

The amounts of HF in the human ureter and PBS in the test tube were determined by HPLC. The mobile phase consisted of 10 mM ammonium acetate buffer (pH adjusted to 4.3 with acetic acid), triethylamine, and acetonitrile. It was delivered to the analytical column according to a gradient program, starting with a composition of ammonium acetate buffer (10 mM, pH 4.7), acetonitrile-triethylamine (70:30:0.2, v/v/v), and changing linearly to ammonium acetate buffer (10 mM, pH 4.7)- acetonitrile-triethylamine (10:90:0.2, v/v/v) over 11 minutes at a flow rate of 1 mL/min.

Stock solutions of HF were prepared at concentrations of 0.5 and 1 mg/mL in 25 mM ammonium acetate buffer (pH 4.3). Working standard solutions were obtained by appropriate dilution with the mobile phase to yield concentrations ranging from 0.2 to 10 µg/mL in human ureter extracts. The stock standard solutions were stable for up to 3 months [22]. A volume of 5 µL of each sample was injected into the HPLC system, and the detection wavelength was set at 243 nm.

Data analysis

Statistical analyses were performed using SPSS software (version 18). Each gel formulation was evaluated using tissue specimens obtained from five independent donors (n = 5 biological replicates per formulation), with each donor representing one independent biological replicate. The influence of gel viscosity and exposure time on halofuginone diffusion was investigated using a two-factor analysis of variance (two-way ANOVA) based on mean values. Tukey's and Bonferroni's post hoc tests were used for multiple comparisons. The level of statistical significance was set at 5% ($P < 0.05$).

Anticipated Outcomes

The model described in our study is expected to provide a reproducible and physiologically relevant ex vivo model for investigating local drug delivery within the urethral wall. By exploiting the histological similarities between the human ureter and urethra, the model enables the evaluation of drug diffusion, tissue retention, and spatial distribution under conditions that closely mimic the native urinary tract environment.

The 3D ureter model is expected to reproduce the tubular geometry of the urethra and to provide valuable information regarding the distribution of locally administered compounds following intraluminal instillation. This approach enables the assessment of the homogeneity of drug exposure throughout the tissue and may help optimize formulation characteristics for targeted local delivery.

Although HF gel was used as a model formulation in the present protocol, the methodology is not restricted to antifibrotic agents. The model may be adapted for the preclinical evaluation of a wide range of intraurethral therapies, including anti-infective, anticancer, regenerative, and anti-inflammatory treatments. By providing a biologically relevant human tissue environment, this ex vivo system may reduce reliance on animal experimentation and facilitate the selection and optimization of candidate formulations before in vivo studies and clinical translation.

Overall, the proposed model is expected to serve as a practical and robust tool for the development of novel therapies targeting urethral diseases and other disorders requiring localized drug delivery within the urinary tract.

5. Conclusion

In conclusion, we have developed a new ex vivo model based on the human ureter, designed to study the diffusion and tissue retention of locally administered compounds in urothelial tissue.

Using a halofuginone gel as a model formulation, the study demonstrated homogeneous tissue distribution and significant tissue retention during the experimental period, with no detectable halofuginone in the recipient compartment. These results confirm the relevance of the proposed model for characterizing the local diffusion of a drug under controlled ex vivo conditions. Although this model does not replicate all the physiological characteristics of the native human urethra, it offers a practical and reproducible experimental platform for the preclinical evaluation and optimization of intraurethral drug delivery systems.

Future studies incorporating assessments of tissue viability, perfusion, and in vivo pharmacokinetic and pharmacodynamic analyses will be necessary to further validate this model's predictive value and establish the therapeutic potential of halofuginone for the treatment of urethral diseases.

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None

Declaration of Competing Interests

The authors declare that they have no conflicts of interest.

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Author contributions

AS, Conceptualization, Formal analysis, Methodology, Writing – Original Draft; NK, Writing – Review & Editing;

BK, Methodology; MJ, Resources; SS, Supervision. All authors contributed to the article and approved the submitted version.

Ethics approval statement

Ethical approval was obtained from the Research Ethics Committee of Sahloul University Hospital, Tunisia (approval No. 13218).

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