

SEÑOR DIRECTOR  
DIRECCIÓN DE NUEVAS CREACIONES  
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO  
E. S. D.

**Asunto:** **Solicitud No.: 15-223660**  
**Oficio No.: 14155**  
**Referencia:** **Respuesta examen de patentabilidad**

MAURICIO JARAMILLO CAMPUZANO, identificado como aparece al pie de mi firma, en calidad de apoderado de la sociedad solicitante **BCN PEPTIDES S.A**, doy respuesta al **Oficio No. 14155**, de conformidad con el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina.

## 1. MODIFICACIONES A LA SOLICITUD

Con el fin de atender las observaciones realizadas por el Examinador, el solicitante aporta un nuevo capítulo reivindicatorio conformado por 4 reivindicaciones en las que se han incluido las siguientes modificaciones:

- 1.1. Se ha restringido el rango correspondiente a la cantidad de la somatostatina en la reivindicación 1 (entre 1 µg/mL y 10 mg/mL).
- 1.2. Se especificó en la reivindicación 1 que la composición es una disolución acuosa isotónica, una disolución acuosa de alcohol polivinílico o sus mezclas, de pH entre 3 y 8.
- 1.3. Es del todo claro que la reivindicación 1 define ahora con mayor limitación las características técnicas esenciales de la composición de la presente invención.
- 1.4. Se eliminaron las antiguas reivindicaciones 2, 4, 5, 6, 9 y 10. La materia de las antiguas reivindicaciones 4, 5, 6 y 10 se han incorporado en la reivindicación 1.

El Solicitante igualmente desea modificar el título de la presente solicitud de la siguiente manera para que el mismo esté acorde con el objeto de las reivindicaciones y con el fin de hacer caso a las sugerencias del Señor Examinador:

*"COMPOSICIÓN TÓPICA OFTÁLMICA DE UNA SOMATOSTATINA"*

Estas modificaciones se ajustan al artículo 34 de la Decisión 486 de 2000 y no constituyen una ampliación de la materia contenida en la solicitud originalmente presentada.

A pesar de eliminar materia del pliego reivindicatorio originalmente presentado, el solicitante no renuncia a la protección que pueda obtener sobre dicha materia y se reserva el derecho de presentar una solicitud divisional que la contenga durante el trámite de la presente solicitud.

## **2. CON RESPECTO A LAS EXCEPCIONES A LA PATENTABILIDAD**

Teniendo en cuenta que la antigua reivindicación 10 no hace parte del nuevo pliego reivindicatorio, se debe dar por superada la objeción relacionada con las excepciones a la patentabilidad.

## **3. CON RESPECTO AL TÍTULO DE LA SOLICITUD**

Considerando que el título ha sido modificado y es ahora consistente con el objeto de las reivindicaciones, definiendo particularmente que la composición tópica oftálmica comprende una somatostatina, la objeción hacia el mismo debe verse superada.

## **4. ARGUMENTOS A FAVOR DE LA CLARIDAD DE LAS REIVINDICACIONES**

- 4.1. Con respecto a la antigua reivindicación 3, relacionada con somatostatina acilada o pegilada, se recuerda al señor Examinador que los ejemplos de la presente solicitud de patente sirven para ilustrar la invención, pero de ninguna manera deben limitar el

alcance de protección de las reivindicaciones. Siendo así las cosas, se debe reconocer que la persona normalmente versada en la materia se encuentra en la capacidad de extrapolar los resultados obtenidos al utilizar una somatostatina, determinado como posibles opciones una somatostatina acilada o pegilada. Por consiguiente, se debe dar por superada esta objeción, amablemente recordándole al Señor Examinador que limitar las reivindicaciones únicamente a lo ejemplificado, resulta en una limitación indebida del alcance de protección de la solicitud.

- 4.2. Adicional a lo anterior, se desea resaltar que la posibilidad de acilación o PEGilación, así como los vehículos y agentes terapéuticos, se han indicado en la descripción. Los métodos de acilación y PEGilación de péptidos son ampliamente conocidos por el experto en la materia, y se realizan de forma habitual buscando mejorar la biodisponibilidad de dichos péptidos. El solicitante quiere aclarar que las mencionadas modificaciones en las somatostatinas no impedirían que la composición realice el efecto técnico de la invención.
- 4.3. Considerando que la antigua reivindicación 9 se ha eliminado del pliego reivindicatorio, se deben dar por superadas todas las objeciones realizadas a dicha cláusula.
- 4.4. Con respecto a los ingredientes objetados, se debe tener en cuenta que con base en los ejemplos de la solicitud y en el contexto proporcionado en la descripción, la persona normalmente versada en la materia se encuentra en la capacidad de seleccionar conservantes, alquil parabenos, alcoholes cetílicos, alcoholes grasos, etc., que sean apropiados para reproducir la invención. Limitar las reivindicaciones a los compuestos ejemplificados llevaría a una restricción indebida de su alcance de protección.

## 5. DETERMINACIÓN DEL ESTADO DE LA TÉCNICA

El Examinador ha determinado que los siguientes documentos anticipan el objeto de la presente solicitud:

- 5.1. *"Medicaments for the treatment of a choroidal neovascularization (CNV) related disorder"*, correspondiente a la solicitud de patente EP1040837 e identificado como D1.
- 5.2. *"Systemic delivery of polypeptides through the eye"*, correspondiente a la solicitud de patente US5283236, e identificado como D2.

## 6. ARGUMENTOS A FAVOR DEL NIVEL INVENTIVO DE LA INVENCIÓN

- 6.1. La nueva reivindicación 1 define todas las características necesarias de una **composición para aplicación tópica oftálmica**, que comprende una somatostatina con una concentración de entre 1 µg/ml y 10 mg/ml y es una disolución isotónica acuosa, una disolución acuosa de alcohol polivinílico o sus mezclas. Esta composición permite el tratamiento efectivo de enfermedades del fondo del ojo por vía tópica, tal y como se demuestra en los ejemplos de la solicitud (Ejemplo 14).
- 6.2. D1 menciona el uso potencial de un compuesto que se une a al menos un receptor de somatostatina en el ojo en la manufactura de un medicamento para el tratamiento de un desorden relacionado con neovascularización coroidea (página 1 [0001], página 3 [0014]). El compuesto puede ser somatostatina o una somatostatina análoga (página 3 [0017]), y la administración puede ser mediante cualquier ruta convencional (página 5 [0025]).
- 6.3. Sin embargo, D1 **no proporciona sugerencia alguna** acerca de las características técnicas de las composiciones farmacéuticas a ser utilizadas. **D1 no menciona o reduce a la práctica ninguna composición específica para la administración ocular tópica.**
- 6.4. Un rango específico de concentración de los compuestos en las composiciones para administración tópica, por ejemplo, no se proporciona en D1. La referencia realizada en D1 a cantidades o dosis para la administración, corresponde específicamente a administración subcutánea de aproximadamente 100 µg a 10 mg por día como una dosis sencilla o en dosis divididas (párrafo [0028]).

Como una modalidad preferida, la administración de octreotida mediante inyección subcutánea se menciona en el mismo párrafo, a una dosis de desde 0.2 mg a 10 mg dos o tres veces al día. Esto resulta en un rango de dosis sistémica administrada de octreotida de 0.4 mg/día a 30 mg/día (suponiendo una biodisponibilidad subcutánea de octreotida del 100%).

- 6.5. Los solicitantes han establecido un rango específico de concentración de la somatostatina específica o el análogo de somatostatina en la reivindicación 1, desde 1 µg/mL a 10 mg/mL, para la administración ocular tópica y un solvente específico o mezclas de solventes, pH **específicamente restringido a administración tópica oftálmica**. Como un ejemplo ilustrativo, la administración de gotas de un volumen aproximado de 40 µL desde 1 a 3 veces por día, resultaría en la administración de péptido en un rango de 0.04 µg/día a 1.2 mg/día. Se debe notar que en la administración tópica, sólo una pequeña parte de la cantidad total administrada alcanzará su objetivo, ya que la disponibilidad de composiciones oftálmicas tópicas es menor al 5% (ver Amo et al. *Drug Discovery Today*, 2008, 13: 135-143; página 135, segunda columna, segundo párrafo). Por estas razones, la dosis activa biodisponible en la presente invención estará en un rango de aproximadamente 0.002 µg-0.06 mg por día o menos en el caso de somatostatinas, lo que es **mucho menor** que la dosis efectiva propuesta por D1.
- 6.6. Por otra parte, D1 referencia concentraciones de 2% a 10% (**p/p**), la cual se encuentra exclusivamente dirigida a formulaciones para retardar la liberación y se refiere al peso de péptido por peso del vehículo. En composiciones de liberación lenta, el vehículo es comúnmente sólido, por ejemplo, un polímero biodegradable. Este rango de concentración no puede ser comparado con el rango divulgado de somatostatina en una solución acuosa para aplicación tópica en el ojo. Incluso en el caso de comparación, el solicitante desea resaltar que:

- una concentración de solución acuosa del **10% (p/p)** es equivalente a una solución de 10 g de péptido /100g de solución, es decir 10g/100 mL o **100 mg/mL**,

- una concentración de solución acuosa del **2% (p/p)** es equivalente a una solución de 2g/100 g, es decir, aproximadamente 2g/100 mL o **20mg/mL**.

6.7. Por consiguiente, **el rango divulgado en D1, 20 mg/mL-100mg/mL es más amplio y considerablemente superior al rango de la reivindicación 1** (1 µg/mL a 10 mg/mL).

6.8. Los solicitantes consideran que la persona con conocimientos en el campo técnico, con base en las enseñanzas de D1, no se vería motivada a utilizar la composición oftálmica tópica de la reivindicación 1 para el tratamiento tópico y/o prevención de enfermedades del segmento posterior del ojo con una expectativa razonable de éxito porque:

- 1) D1 no divulga composiciones específicas para tratamiento ocular, ni mucho menos una composición oftálmica tópica, y no proporciona de forma específica ningún rango de concentraciones de los compuestos que puedan ser utilizadas de forma tópica. El rango de concentraciones dado para formulaciones de administración subcutánea y liberación lenta es muy amplio y mucho más elevado que el rango divulgado en la reivindicación 1.
- 2) D1 no soluciona los problemas del estado de la técnica, relacionados con las dificultades para la administración de composiciones oftálmicas para el tratamiento de enfermedades del segmento posterior del ojo (ver la descripción del estado de la técnica de la presente solicitud). La ruta de administración sistémica en el segmento posterior del ojo usualmente no alcanza concentraciones terapéuticas en el segmento posterior del ojo, debido a la barrera hemato-retinal. Más aún, el efecto de la medicación no es local. En el caso de somatostatina, altas dosis serían necesarias dada su inestabilidad en la sangre.

- 6.9. D2 divulga composiciones y métodos para la entrega sistémica de polipéptidos tales como la insulina o el glucagón a través de los ojos, mediante absorción en el conducto nasolacrimal (Resumen; D2, columna 3, tercer párrafo). Un agente que mejora la penetración es necesario para mejorar la absorción del polipéptido a la circulación sistémica (reivindicación 1), especialmente en polipéptidos que tienen pesos moleculares que exceden 5000 (columna 8, líneas 36-63).
- 6.10. Los polipéptidos llegan a la circulación sistémica mediante absorción en el conducto nasolacrimal, pero la llegada del polipéptido al segmento posterior del ojo no se garantiza. La aplicación del péptido en el ojo mediante instalación tópica, que lleva a la absorción a la circulación sistémica (Figuras de D2), demuestra prácticamente una absorción nula de péptido al segmento posterior del ojo, tal como la retina (Tablas 2 a 9 de D2). La cantidad de péptidos en el tejido del ojo fue muy bajo, menos en la córnea, en donde los péptidos habían estado en contacto directo cuando se aplicaron (columna 20, últimas 3 líneas).
- 6.11. Por consiguiente, **D2 confirma que los polipéptidos administrados tópicamente en el ojo, no alcanzan el segmento posterior del ojo.**
- 6.12. D2 divulga que la concentración del péptido en la composición no debe exceder 10% (p/v) para no perturbar el ambiente isotónico del ojo (columna 8, líneas 20 a 25). El solicitante desea resaltar que una solución de concentración **10% (p/v)** es una solución de 10g / 100 mL, es decir **100mg/mL, una concentración mucho más alta y alejada al rango de la nueva reivindicación 1** (1 µg/mL a 10 mg/mL).
- 6.13. Por ende, la combinación de un rango más angosto de somatostatina, el solvente específico y el pH de la composición para administración oftálmica tópica de la presente reivindicación 1, hace que esta misma sea novedosa e inventiva con respecto a los documentos D1 y D2.
- 6.14. La composición de la presente invención soluciona ambos problemas de las composiciones del estado de la técnica relativos al confort del

paciente, especialmente en el caso de inyecciones intravítreas, y la baja disponibilidad terapéutica de la administración sistémica mediante inyección. El uso de gotas para los ojos, y la ruta tópica en general, no han sido considerados como una ruta apropiada para la administración de medicamentos que pretendan prevenir o arrestar las enfermedades de retina, gracias a la **suposición general de que no alcanzan la cámara posterior del ojo**. El camino ocular tópico, como una ruta para la administración de medicamentos, cuyo objetivo es el segmento posterior del ojo, ha sido limitado hasta el momento, debido a la estimación de que el porcentaje de sustancia activa capaz alcanzar el segmento posterior es insignificante en la mayoría de casos, como se divulga en el estado de la técnica de la presente solicitud.

- 6.15. Se debe ver también, por ejemplo, el artículo de Raghava et al. *Expert Opinion on Drug Delivery*, 2004, 1: 99-114. Raghava, el cual divulga que "La entrega de concentraciones terapéuticas de fármacos a la retina sigue siendo un desafío para los científicos farmacéuticos debido a las barreras anatómicas y fisiológicas asociadas con este tejido "(página 99, líneas 3-6 del párrafo Introducción) y" Para los medicamentos administrados por vía tópica, La córnea y la conjuntiva son las principales barreras para la entrada de fármacos oculares. Estas barreras, junto con el drenaje nasolacrimal de las gotas administradas, el metabolismo del fármaco, la unión a las proteínas, la barrera de las lentes y las largas trayectorias de difusión, **resultan en un suministro pobre de fármacos a la retina después de la administración tópica**" (página 99, líneas 8-15 del párrafo Introducción). Otro ejemplo puede encontrarse en la revisión de del Amo et al. *Drug Discovery Today*, 2008, 13: 135-143. Como se indica en el resumen del Amo, "la administración tópica de la gota ocular es útil solamente para el tratamiento de las enfermedades del segmento anterior. El segmento posterior del ojo es un objetivo terapéutico importante con necesidades médicas no cubiertas"; El último párrafo de la página 135 enseña que "las gotas oculares se usan sólo para el tratamiento de trastornos del segmento anterior, ya que no se alcanzan las concentraciones adecuadas de fármaco en los tejidos posteriores usando este método de administración de fármaco".

- 6.16. Además, Urtti et al. in *"Challenges and obstacles of ocular pharmacokinetics and drug delivery"*, Adv. Drug Deliv. Rev. 2006, 58: 1131-1135, divulga la administración tópica de fármacos oculares *"a través de la conjuntiva y más allá del segmento posterior sería deseable, pero desafortunadamente la penetración es clínicamente insignificante"* (página 1134, segunda columna, primer párrafo).
- 6.17. **D2 también confirma la suposición aceptada en el estado de la técnica de acuerdo con la cual medicamentos tópicamente administrados en el ojo, no alcanzan el segmento posterior del ojo y no permiten el tratamiento de enfermedades de retina.**
- 6.18. De acuerdo con lo anterior, la persona normalmente versada en la materia, siguiendo la suposición aceptada de conocimiento general y el estado de la técnica que divulga medicamentos que no alcanzan la cámara posterior del ojo cuando se administran por ruta ocular tópica, **no hubiera estado motivada** a preparar una composición tópica oftálmica de baja concentración de somatostatinas, capaz de alcanzar el segmento posterior del ojo y tratar enfermedades de retina, como la que se divulga en la reivindicación 1 de la presente solicitud. De hecho, la persona con conocimientos medios en el campo técnico se vería desmotivada para hacerlo, en vista de las enseñanzas del estado de la técnica y específicamente D1 y D2.
- 6.19. Se considera igualmente que la invención reivindicada representa un avance prominente sobre el estado de la técnica, y resuelve una necesidad existente desde hace algún tiempo en las clínicas y en la industria farmacéutica. La composición de la reivindicación 1 es la primera composición oftálmica tópica que pretenden alcanzar el segmento posterior del ojo. De hecho, la somatostatina, mediante cualquier ruta de administración, nunca ha sido divulgada como útil en un posible tratamiento de enfermedades del segmento posterior del ojo. Todos estos hechos son claros indicios de nivel inventivo.
- 6.20. El primer ensayo clínico con una composición oftálmica tópica contiene un péptido (gotas para ojos de somatostatina) para la

prevención de una enfermedad del segmento posterior del ojo ha sido llevado a cabo por el solicitante de la presente solicitud: *Trial to Assess the Efficacy of Neuroprotective Drugs Administered Topically to Prevent or Arrest Diabetic Retinopathy* (EUROCONDOR, [www.eurocondor.eu](http://www.eurocondor.eu)). En este ensayo con resultados prometedores, **una composición oftálmica de somatostatina** se administra en una aproximación **completamente nueva** para pacientes diabéticos, sin daño microvascular ocular para determinar su eficacia para prevenir o arrestar neurodegeneración de la retina, como también el desarrollo y progreso de etapas tempranas de retinopatía diabética.

6.21. Además, el solicitante desea resaltar que las solicitudes de patente correspondientes han sido concedidas por las oficinas de patentes Europea, Estadounidense, Japonesa, China, Canadiense, entre otras.

6.22. Teniendo en cuenta lo anterior, amablemente se solicita a su Despacho reconocer que las nuevas reivindicaciones 1 a 4 sí tienen nivel inventivo, toda vez que no se ven anticipadas por D1, D2 o su combinación.

## 7. PETICIÓN

Teniendo en cuenta que se ha dado respuesta a todas las observaciones realizadas por su Despacho, demostrando que el nuevo pliego reivindicatorio cumple con los requisitos de patentabilidad, amablemente se solicita proceder al otorgamiento de la solicitud de patente.

## 8. ANEXOS

Adjunto al presente escrito:

- Nuevo pliego reivindicatorio conformado por 4 reivindicaciones.
- Urtti et al. in “*Challenges and obstacles of ocular pharmacokinetics and drug delivery*”, Adv. Drug Deliv. Rev. 2006, 58: 1131-1135
- Amo et al. *Drug Discovery Today*, 2008, 13: 135-143
- Raghava et al. *Expert Opinion on Drug Delivery*, 2004, 1: 99-114

## 9. NOTIFICACIONES

Recibiré notificaciones en la secretaría de su Despacho; en mis oficinas de abogado ubicadas en la Calle 67 No. 7 – 35, oficina 1204, teléfono 3192900, fax 3210295, Bogotá D.C., Colombia, o; al correo electrónico [patentes@gpzlegal.com](mailto:patentes@gpzlegal.com).

Atentamente,



**MAURICIO JARAMILLO C.**

**C.C. 80.421.942 de Bogotá**

**T.P. 74.555 del C.S.J.**

GEC

## **REIVINDICACIONES MODIFICADAS**

1. Composición tópica oftálmica seleccionada del grupo formado por colirios, pomadas y ungüentos, caracterizada por que comprende una cantidad entre 1 µg/mL y 10 mg/mL de una somatostatina seleccionada del grupo formado por somatostatina-28, somatostatina-14, somatostatina-13, prosomatostatina y sus sales farmacéuticamente aceptables, y donde la composición es una disolución acuosa isotónica, una disolución acuosa de alcohol polivinílico o sus mezclas de pH entre 3 y 8, terapéuticamente eficaz en el tratamiento y/o prevención de una enfermedad del segmento posterior del ojo seleccionada del grupo formado por retinopatía diabética no-proliferativa, retinopatía diabética proliferativa, neurodegeneración retiniana, neovascularización de retina, retinopatía inducida por isquemia, retinopatía de la prematuridad, retinopatía de células falciformes, oclusión de la vena retinal, retinitis pigmentosa, uveítis, edema macular y edema macular cistoide.
2. Composición tópica oftálmica según la reivindicación 1, caracterizada por que dicha somatostatina o análogo de somatostatina están sustituidos con un grupo acilo o una unidad de polietilenglicol.
3. Composición tópica oftálmica según la reivindicación 1, dicha composición oftálmica contiene un conservante seleccionado del grupo formado por cloruro de benzalconio, ácido benzoico, alquil parabenos, alquil benzoatos, clorobutanol, clorocresol, alcoholes cetílicos, alcoholes grasos como hexadecil alcohol, compuestos organometálicos de mercurio, como acetato, nitrato o borato de fenilmercurio, diazolidinil urea, adipato de diisopropilo, dimetil polisiloxano, sales de EDTA, vitamina E y sus mezclas.
4. Composición tópica oftálmica según la reivindicación 1, dicha composición oftálmica contiene un agente que aumenta la permeabilidad de dicha somatostatina y análogo de somatostatina seleccionado del grupo formado por cloruro de benzalconio, saponinas, ácidos grasos, éteres grasos de polioxietileno, ésteres alquílicos de ácidos grasos, pirrolidonas, polivinilpirrolidona, ácidos pirúvicos, ácidos piroglutámicos y sus mezclas.

# Challenges and obstacles of ocular pharmacokinetics and drug delivery<sup>☆</sup>

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Received 12 June 2006; accepted 31 July 2006

Available online 26 September 2006

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## Abstract

Modern biological research has produced increasing number of promising therapeutic possibilities for medical treatment. These include for example growth factors, monoclonal antibodies, gene knockdown methods, gene therapy, surgical transplantations and tissue engineering. Ocular application of these possibilities involves drug delivery in many forms. Ocular drug delivery is hampered by the barriers protecting the eye. This review presents an overview of the essential factors in ocular pharmacokinetics and selected pharmacological future challenges in ophthalmology.

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**Keywords:** Pharmacokinetics; Eye; Drug delivery; Epithelial barriers; Posterior segment

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<sup>☆</sup> This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Ocular Drug Delivery", Vol. 58/11, 2006.

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## 1. Introduction

In clinical practice the anterior segment of the eye (cornea, conjunctiva, sclera, anterior uvea) can be treated with topical ocular eye drops, the most commonly used dosage form in ocular drug treatment. Unfortunately the eye drops are rapidly drained from the ocular surface and, therefore, the time for drug absorption is only a few minutes and bioavailability is very low, typically less than 5% [1]. Bioavailability and duration of activity may be increased modestly by prolonged action dosage forms, but they have not gained wide acceptance by the patients. Even from the modified formulations the ocular drug absorption is limited by the corneal and conjunctival epithelial barriers of the eye [1].

Topical ocular medications do not reach the posterior segment drug targets. Posterior segment (retina, vitreous, choroid) can be treated by high drug doses given intravenously or by intravitreal administration. Currently there is rapidly growing interest in the posterior segment drug delivery [2]. This is caused by the advances in the understanding of the pathophysiological processes in the retina and choroid. Many posterior segment diseases cannot be treated effectively with current methods. These diseases include age related macular degeneration, retinitis pigmentosa, diabetic retinopathies, and neural changes induced by glaucoma. Posterior segment delivery of both small molecules and larger bio-organic compounds, such as proteins and DNA, is problematic. Only drugs with wide therapeutic index (such as antibiotics) can be given in massive doses to blood stream to treat the posterior segment. Intravitreal injection, on the other hand, is invasive method and may cause even endophthalmitis. Therefore, it is not considered to be an ideal method of drug administration to large numbers of patients. Therefore, there is increasing interest to develop new prolonged action dosage forms for subconjunctival and periocular administration. Another option is efficient drug targeting from the blood stream to the retinal pigment epithelium or choroidal vasculature. Breakthroughs in such approaches should enable more patient friendly, safer and efficient treatment of posterior segment diseases with antibodies, oligonucleotides, genes, and growth factors. Even though the main emphasis in current ocular drug delivery research is focused on posterior eye segment, there are still challenges remaining. For example the treatment of lacrimal gland and the

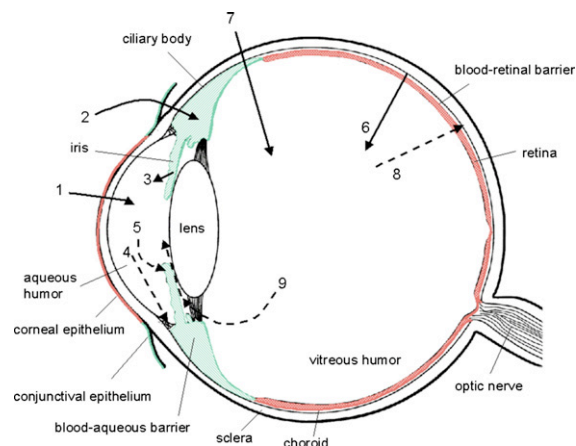


Fig. 1. Schematic presentation of the ocular structure with the routes of drug kinetics illustrated. The numbers refer to following processes: 1) transcorneal permeation from the lacrimal fluid into the anterior chamber, 2) non-corneal drug permeation across the conjunctiva and sclera into the anterior uvea, 3) drug distribution from the blood stream via blood-aqueous barrier into the anterior chamber, 4) elimination of drug from the anterior chamber by the aqueous humor turnover to the trabecular meshwork and Schlemm's canal, 5) drug elimination from the aqueous humor into the systemic circulation across the blood-aqueous barrier, 6) drug distribution from the blood into the posterior eye across the blood-retina barrier, 7) intravitreal drug administration, 8) drug elimination from the vitreous via posterior route across the blood-retina barrier, and 9) drug elimination from the vitreous via anterior route to the posterior chamber.

disorders of lacrimal secretion are still poorly understood fields.

Comprehensive reviews about drug delivery and pharmacokinetics of the eye have been published earlier [1,3,4]. Therefore, this review provides only an overview of the main aspects of ocular pharmacokinetics. This chapter should serve as an introduction to the following chapters of this theme issue.

## 2. Ocular pharmacokinetics

The main routes of drug administration and elimination from the eye have been shown schematically in Fig. 1.

### 2.1. The barriers

#### 2.1.1. Drug loss from the ocular surface

After instillation, the flow of lacrimal fluid removes instilled compounds from the surface of the eye. Even

though the lacrimal turnover rate is only about 1  $\mu\text{L}/\text{min}$  the excess volume of the instilled fluid is flown to the nasolacrimal duct rapidly in a couple of minutes [5]. Another source of non-productive drug removal is its systemic absorption instead of ocular absorption. Systemic absorption may take place either directly from the conjunctival sac via local blood capillaries or after the solution flow to the nasal cavity [6,7]. Anyway, most of small molecular weight drug dose is absorbed into systemic circulation rapidly in few minutes. This contrasts the low ocular bioavailability of less than 5% [5].

Drug absorption into the systemic circulation decreases the drug concentration in lacrimal fluid extensively. Therefore, constant drug release from solid delivery system to the tear fluid may lead only to ocular bioavailability of about 10%, since most of the drug is cleared by the local systemic absorption anyway [8].

#### 2.1.2. *Lacrimal fluid-eye barriers*

Corneal epithelium limits drug absorption from the lacrimal fluid into the eye [1]. The corneal barrier is formed upon maturation of the epithelial cells. They migrate from the limbal region towards the center of the cornea and to the apical surface. The most apical corneal epithelial cells form tight junctions that limit the paracellular drug permeation [4]. Therefore, lipophilic drugs have typically at least an order of magnitude higher permeability in the cornea than the hydrophilic drugs [9]. Despite the tightness of the corneal epithelial layer, transcorneal permeation is the main route of drug entrance from the lacrimal fluid to the aqueous humor (Fig. 1).

In general, the conjunctiva is more leaky epithelium than the cornea and its surface area is also nearly 20 times greater than that of the cornea [10,11]. Drug absorption across the bulbar conjunctiva has gained increasing attention recently, since conjunctiva is also fairly permeable to the hydrophilic and large molecules [12]. Therefore, it may serve as a route of absorption for larger bio-organic compounds such as proteins and peptides. Clinically used drugs are generally small and fairly lipophilic. Thus, the corneal route is currently dominating.

In both membranes, cornea and conjunctiva, principles of passive diffusion have been extensively investigated, but the role of active transporters is only sparsely studied.

#### 2.1.3. *Blood-ocular barriers*

The eye is protected from the xenobiotics in the blood stream by blood-ocular barriers. These barriers have two

parts: blood-aqueous barrier and blood-retina barrier (Fig. 1).

The anterior blood-eye barrier is composed of the endothelial cells in the uvea. This barrier prevents the access of plasma albumin into the aqueous humor, and limits also the access of hydrophilic drugs from plasma into the aqueous humor. Inflammation may disrupt the integrity of this barrier causing the unlimited drug distribution to the anterior chamber. In fact, the permeability of this barrier is poorly characterised.

The posterior barrier between blood stream and eye is comprised of retinal pigment epithelium (RPE) and the tight walls of retinal capillaries [1,4]. Unlike retinal capillaries the vasculature of the choroid has extensive blood flow and leaky walls. Drugs easily gain access to the choroidal extravascular space, but thereafter distribution into the retina is limited by the RPE and retinal endothelia. Despite its high blood flow the choroidal blood flow constitutes only a minor fraction of the entire blood flow in the body. Therefore, without specific targeting systems only a minute fraction of the intravenous or oral drug dose gains access to the retina and choroid.

Unlike blood brain barrier, the blood-eye barriers have not been characterised in terms of drug transporter and metabolic enzyme expression. From the pharmacokinetic perspective plenty of basic research is needed before the nature of blood-eye barriers is understood.

#### 2.2. *Routes of ocular drug delivery*

There are several possible routes of drug delivery into the ocular tissues (Fig. 1). The selection of the route of administration depends primarily on the target tissue. Traditionally topical ocular and subconjunctival administrations are used for anterior targets and intravitreal administration for posterior targets. Design of the dosage form can have big influence on the resulting drug concentrations and on the duration of drug action.

##### 2.2.1. *Topical ocular*

Typically topical ocular drug administration is accomplished by eye drops, but they have only a short contact time on the eye surface. The contact, and thereby duration of drug action, can be prolonged by formulation design (e.g. gels, gelifying formulations, ointments, and inserts) [4].

During the short contact of drug on the corneal surface it partitions to the epithelium and in the case of lipophilic compounds it remains in the epithelium and is slowly released to the corneal stroma and further to the anterior chamber [13]. After eye drop administration the peak concentration in the anterior chamber is reached after 20–30 min, but this concentration is typically two orders of magnitude lower than the instilled concentration even for lipophilic compounds [8]. From the aqueous humor the drug has an easy access to the iris and ciliary body, where the drug may bind to melanin. Melanin bound drug may form a reservoir that is released gradually to the surrounding cells, thereby prolonging the drug activity. Distribution to the lens is much slower than the distribution to the uvea [1]. Unlike porous uvea, the lens is tightly packed protein rich structure where drug partitioning takes place slowly.

Drug is eliminated from the aqueous humor by two main mechanisms: by aqueous turnover through the chamber angle and Schlemm's canal and by the venous blood flow of the anterior uvea [1] (Fig. 1). The first mechanism has a rate of about 3  $\mu\text{l}/\text{min}$  and this convective flow is independent of the drug. Elimination by the uveal blood flow, on the other hand, depends on the drug's ability to penetrate across the endothelial walls of the vessels. For this reason, clearance from the anterior chamber is faster for lipophilic than for hydrophilic drugs. Clearance of lipophilic drugs can be in the range of 20–30  $\mu\text{l}/\text{min}$ . In those cases, most of drug elimination takes place via uveal blood flow. Half-lives of drugs in the anterior chamber are typically short, about an hour. The volumes of distribution are difficult to determine due to the slow equilibration of drug in the ocular tissues. The estimates in rabbits range from the volume of aqueous humor (250  $\mu\text{l}$ ) up to 2 ml [4]. In the latter case, the slow drug distribution to the vitreous is included in the volume of distribution. This distribution is slow, because the lens prohibits drug access to the vitreous. Flow of aqueous humor from the posterior chamber to the anterior chamber is another limiting factor.

Some part of topically administered drugs may absorb across the bulbar conjunctiva to the sclera and further to the uvea and posterior segment (Fig. 1). This is an inefficient process, but may be improved by dosage forms that release drug constantly to the conjunctival surface. The role of this non-corneal route of absorption depends on the drug properties. Generally more hydrophilic and

larger molecules may absorb via this route. They have particularly poor penetration across the cornea, and therefore, the relative contribution of the non-corneal is more eminent. Delivery across the conjunctiva and further to the posterior segment would be desirable, but unfortunately the penetration is clinically insignificant.

#### *2.2.1.1. Subconjunctival administration.*

Traditionally subconjunctival injections have been used to deliver drugs at increased levels to the uvea. Currently this mode of drug delivery has gained new momentum for various reasons. The progress in materials sciences and pharmaceutical formulation have provided new exciting possibilities to develop controlled release formulations to deliver drugs to the posterior segment and to guide the healing process after surgery (e.g. glaucoma surgery) [14]. Secondly, the development of new therapies for macular degeneration (antibodies, oligonucleotides) must be delivered to the retina and choroid [15,16].

After subconjunctival injection drug must penetrate across sclera which is more permeable than the cornea. Interestingly the scleral permeability is not dependent on drug lipophilicity [10,17]. In this respect it clearly differs from the cornea and conjunctiva. Even more interesting is the surprisingly high permeability of sclera to the large molecules of even protein size [18]. Thus, it would seem feasible to deliver drugs across sclera to the choroid. However, delivery to the retina is more complicated, because in this case the drug must pass across the choroid and RPE. The role of blood flow is well characterised kinetically but the based on the existing information, there are good reasons to believe that drugs may be cleared significantly to the blood stream in the choroid. Pitkänen et al. showed recently that RPE is tighter barrier than sclera for the permeation of hydrophilic compounds [17]. In the case of small lipophilic drugs they have similar permeabilities.

More complete understanding of the kinetics in sclera, choroid and RPE should help to develop medications with optimal activity in the selected posterior target tissues. Combination of the kinetic knowledge and cell selective targeting moieties offer very interesting possibilities.

#### *2.2.1.2. Intravitreal administration.*

Direct drug administration into the vitreous offers distinct advantage of more straightforward access to the vitreous and retina (Fig. 1). It should be noted, however,

that delivery from the vitreous to the choroid is more complicated due to the hindrance by the RPE barrier. Small molecules are able to diffuse rapidly in the vitreous but the mobility of large molecules, particularly positively charged, is restricted [19]. Likewise, the mobility of the nanoparticles is highly dependent on the structure. In addition to the diffusive movement convection also plays a role [20]. The convection results from the eye movements.

After intravitreal injection the drug is eliminated by two main routes: anterior and posterior [1]. All compounds are able to use the anterior route. This means drug diffusion across the vitreous to the posterior chamber and, thereafter, elimination via aqueous turnover and uveal blood flow. Posterior elimination takes place by permeation across the posterior blood-eye barrier. This requires adequate passive permeability (i.e. small molecular size, lipophilicity) or active transport across these barriers. For these reasons, large molecular weight and water-solubility tend to prolong the half-life in the vitreous [1].

Drugs can be administered to the vitreous also in controlled release formulations (liposomes, microspheres, implants) to prolong the drug activity.

### 3. Conclusions

Ocular pharmacokinetics and drug delivery issues were shortly described. It is evident that there are major obstacles in ocular pharmacokinetics. Overcoming these barriers should help in the development of improved drug delivery systems to treat conditions with currently unmet medical need.

### Acknowledgement

This study was supported by the Academy of Finland.

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# Current and future ophthalmic drug delivery systems

## A shift to the posterior segment

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Topical eye drop administration is useful only for the treatment of anterior segment diseases. The posterior eye segment is an important therapeutic target with unmet medical needs. The leading causes of visual impairment in the industrial countries are related to the disorders in the posterior eye tissues. New drugs for the medication of the posterior ocular segment have emerged, but most drugs are delivered by repeated intravitreal injections. Effective, safe, and comfortable methods of drug delivery are needed. The emerging methods include polymeric-controlled release injections and implants, nanoparticulates, microencapsulated cells, iontophoresis, and gene medicines. The biggest drug delivery challenge is to develop effective methods for posterior segment therapies that would also be applicable for the out-patient use.

### Introduction

Posterior segment ocular diseases are the most prevalent causes of visual impairment in the industrial countries. These diseases include, for example, age-related macular degeneration and diabetic retinopathy. However, the ocular drug market is dominated by anterior segment drug therapies (e.g. antibiotics, anti-inflammatory agents, diagnostics, and intraocular pressure decreasing anti-glaucoma drugs), typically in eye drop formulations.

The rapid progress of the biosciences opens new possibilities to meet the needs of the posterior segment treatments. The examples include the antisense and aptamer drugs for the treatment of cytomegalovirus (CMV) retinitis and age-related macular degeneration, respectively, and the monoclonal antibodies for the treatment of the age-related macular degeneration. These compounds are given as intravitreal injections to the patients. Other new approaches for the treatment of macular degeneration and inherited retinal degenerations include intravitreal small interfering RNA (siRNA) and gene therapy, respectively.

This review will give an update and the recent progress and trends in ocular drug delivery systems.

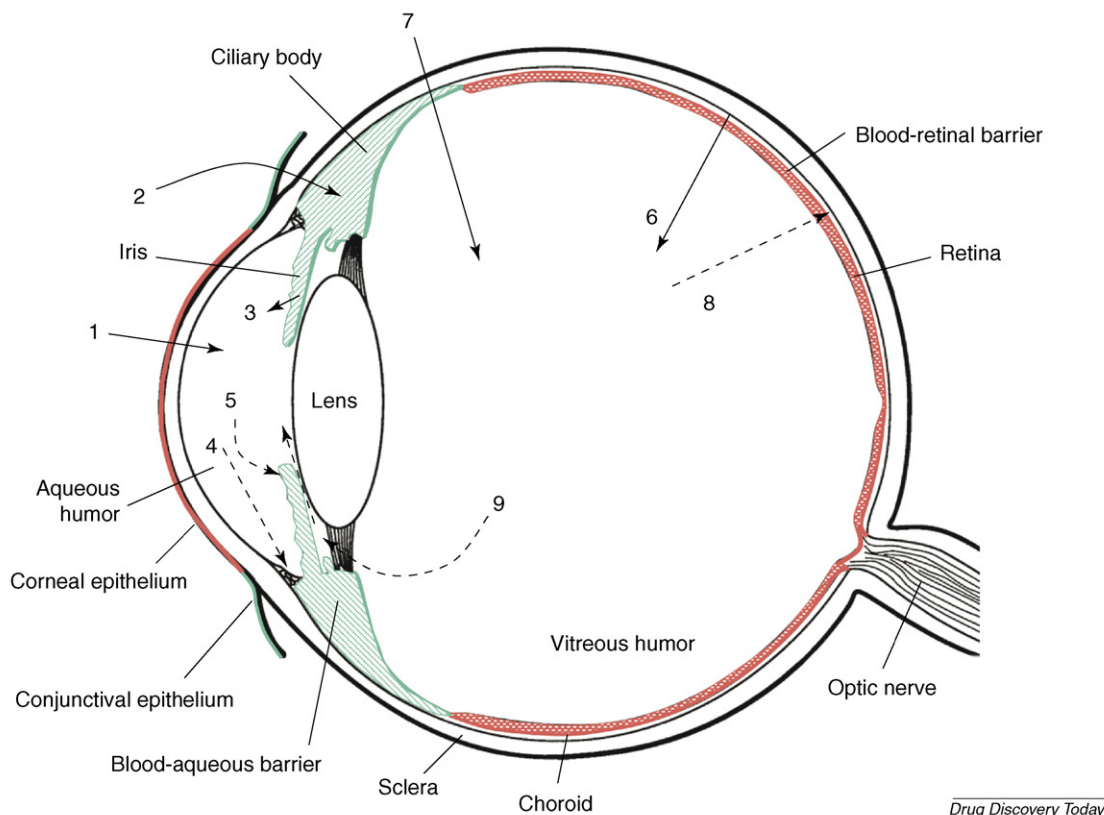
### Ocular pharmacokinetics: barriers in drug delivery

The ocular tissues can be reached either by local or systemic drug administration. The tissue barriers limit the access of drugs to their targets [1] (Figure 1). The corneal and conjunctival epithelial barriers cover the ocular surface. The blood–aqueous barrier, composed of the uveal capillary endothelia and ciliary epithelia, limits the access of compounds from the systemic circulation to the anterior chamber, whereas the blood–retina barrier limits the drug diffusion from the systemic blood to the retina and vice versa. The barrier has two components: outer and inner blood–retina barriers that are formed by the retinal pigment epithelium (RPE) and the tight retinal capillary walls, respectively.

After topical eye drop administration only less than 5% of the dose is absorbed into the eye [2]. The dose is mostly absorbed to the systemic blood circulation via the conjunctival and nasal blood vessels. For example, at least 70% of the timolol dose is systemically absorbed within 5 min [2,3]. Ocular absorption is limited by the corneal epithelium, and it is only modestly increased by prolonged ocular contact. Owing to the extensive conjunctival systemic absorption the maximal attainable ocular absorption is only about 10% of the dose [2].

Eye drops are used only for the treatment of the anterior segment disorders, since adequate drug concentrations are not reached in the posterior tissues using this drug delivery method.

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**FIGURE 1**

Schematic presentation of the ocular structure with the routes of drug kinetics illustrated. The numbers refer to following processes: (1) trans-corneal permeation from the lacrimal fluid into the anterior chamber, (2) non-corneal drug permeation across the conjunctiva and sclera into the anterior uvea, (3) drug distribution from the blood stream via blood–aqueous barrier into the anterior chamber, (4) elimination of drug from the anterior chamber by the aqueous humor turnover to the trabecular meshwork and Schlemm's canal, (5) drug elimination from the aqueous humor into the systemic uveoscleral circulation, (6) drug distribution from the blood into the posterior eye across the blood–retina barrier, (7) intravitreal drug administration, (8) drug elimination from the vitreous via posterior route across the blood retina barrier, and (9) drug elimination from the vitreous via anterior route to the posterior chamber [1].

The drug concentration difference between the cornea and retina is several orders of magnitude [2]. After administration in eye drops, most clinically used drugs are absorbed across the cornea to the anterior chamber (Figure 1). The non-corneal route, via conjunctiva and sclera, avoids the counter flow of aqueous humor and the lens barrier. Therefore, this route may be a viable future alternative for the administration of drugs (including proteins and gene-based drugs) to the retina and vitreous if appropriate delivery systems are developed. The sclera is permeable even to macromolecules, but choroidal blood flow and RPE are the major barriers in drug penetration [4,5].

Intravitreal injection can provide adequate drug concentrations in the posterior segment. Owing to the invasive nature of the injection, it is important to design drug formulations to maintain the therapeutic drug concentration over prolonged periods and minimize the number of injections. Drugs are eliminated via the anterior route, that is, to the aqueous humor and then eliminated by the outflow of the humor in the anterior chamber angle [6]. Many drugs are also eliminated posteriorly through the blood–retina barrier to the systemic circulation. Such drugs must have adequate permeability (i.e. lipophilicity or active transport) in the retinal capillaries and in the RPE [6]. In this case, the half-life of the drugs becomes short, even 2–3 h.

Finally, drugs may be delivered to the posterior ocular segment from the systemic blood circulation. Again, permeable drugs can cross the blood–retina barrier to reach the retina and vitreous [6]. Access to the choroid is easier owing to the extensive blood flow and leaky vessels in this tissue. Only a small fraction of the blood flow circulates through the posterior ocular segment. Therefore, high doses are needed and systemic adverse effects are common (e.g. systemic treatment of glaucoma with carbonic anhydrase inhibitors). Such approach is not feasible for potent drugs with narrow therapeutic indices. Localized targeting of such drugs to specific cells in the choroid, RPE, or retinal capillaries is an appealing approach.

### Evolution of ocular drug delivery systems

Eye drops have already been used at the times of Cleopatra for the treatment of ocular conditions. For example, *Belladonna* (i.e. atropine) was used as a mydriatic in ancient Egypt. The eye drops must be administered frequently, their ocular bioavailability is low (less than 5% of the dose is absorbed), and the posterior segment cannot be treated with them. For these reasons, prolonged action dosage forms with improved ocular absorption have been developed. The first polymeric inserts that release the drug over prolonged period were used already in the late 1800s in the U.K. These

gelatine inserts released cocaine for the purpose of local ocular anesthesia. Soluble ophthalmic drug inserts (SODI) were introduced in the 1960s in the Soviet Union. They were manufactured as several versions that contained drugs such as pilocarpine and mydriatics. The matrix of an acrylate-based co-polymer dissolved during a couple of hours after its application to the conjunctival sac. Pilocarpine releasing Ocuser<sup>®</sup> (Alza, USA) was introduced in the early 1970s in the Western world. This sophisticated system released the drug for a week at constant rate of 40 µg/h through ethylene vinyl acetate (EVA) membranes [7]. Later, another insert, Lacrisert<sup>®</sup> (Merck and Co. Inc., USA), was introduced for the treatment of dry eye syndrome [8]. These inserts did not become popular in the out-patient use because the elderly patients had difficulties to use them, and occasionally the insert was expelled from the conjunctival sac during sleep. This motivated the development of liquid state delivery system that forms a timolol releasing gel after its instillation as an eye drop [9]. Another product releases betaxolol to the tear fluid by ion-exchange from the surface of microspheres [10]. These approaches can modestly delay drug release and prolong drug action. Drug immersed hydrophilic contact lenses and topical ocular liposomes have been tested for drug delivery already in the 1970s and 1980s, but these approaches resulted only in limited improvements [11]. Importantly, the posterior ocular tissues cannot be treated with these topical ocular delivery methods.

The need to treat the posterior segment of the eye revived the interest in ocular-controlled release systems. Vitrasert<sup>®</sup> (Bausch &

Lomb, USA), a polymeric ganciclovir implant, was introduced already in the 1990s for the treatment of opportunistic viral retinitis in the AIDS patients. Most research efforts are currently directed toward the dosage forms to treat the age-related macular degeneration and other retinal diseases.

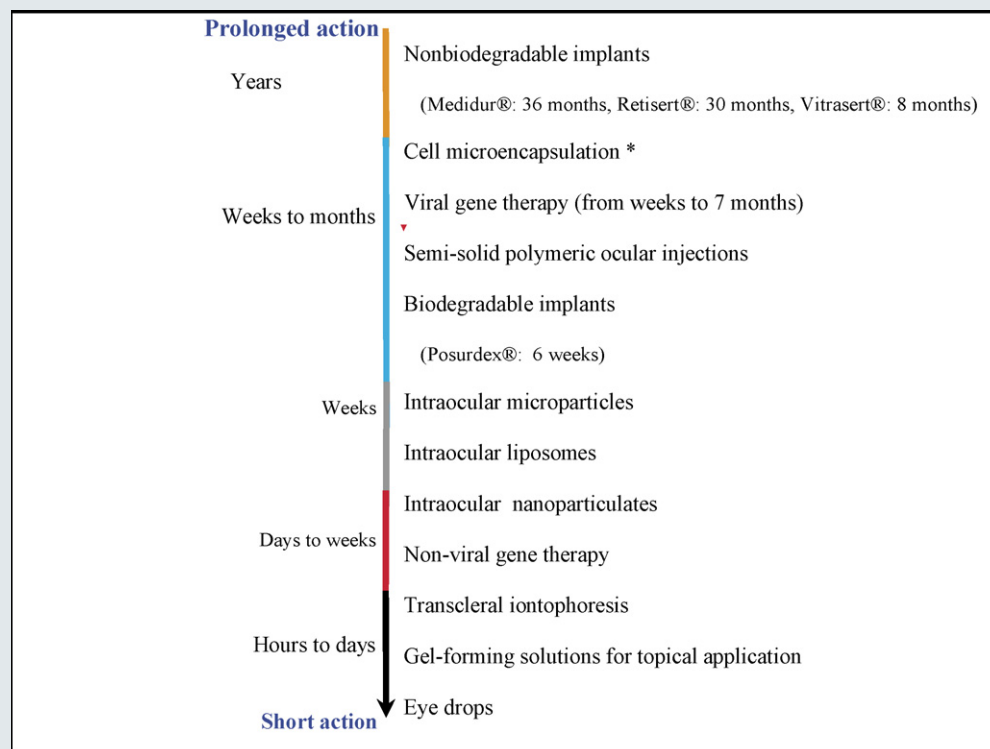
### Current status

Nowadays, there are, on the market or undergoing clinical trials, ocular drug delivery systems designed to sustain drug release. Most of them are for the treatment of long-term diseases that affect the posterior segment of the eye [12]. The important indications for ocular drug delivery systems include macular degeneration, viral infections (like CMV infections), glaucoma, ocular inflammations, dry eye syndrome, and retinal degenerations. There are many important indications for ocular drug delivery systems depending on the site of application and the delivered drug.

The challenge is to provide a system with improved ocular drug bioavailability and prolonged duration of activity (Box 1), but still with a minimum risk of ocular complications (Box 2). The mode of administration plays an important role in defining the safety of the device [13] (Table 1) and further, in achieving patient compliance and acceptance. In general the highest risk of ocular complications is with the invasive intraocular drug delivery. The risk is smaller with periocular drug administration. Ocular complications are rare for the systemic drug administration, but the systemic adverse effects are more prevalent.

#### BOX 1

##### Duration of action of the ocular drug delivery systems



\*To date, the only clinically tested formulation of microencapsulated cells has been implanted for six months in humans, and 18 months in rabbit eyes. Nevertheless, microencapsulated cells have potential for longer periods of implantation and action.

**BOX 2****Classification of the routes for ocular drug administration****Invasive drug administration to intraocular cavities**

Intravitreal surgery (at the pars plana)  
 Repeated<sup>a</sup> intravitreal injections  
 Intracameral surgery (capsular bag)  
 Subretinal injection  
 Repeated<sup>a</sup> suprachoroidal injections  
 Repeated<sup>a</sup> intracameral injections

**Invasive periocular and scleral modes of drug administration**

Intrascleral surgery  
 Episcleral surgery  
 Repeated<sup>a</sup> periocular injections  
 Repeated<sup>a</sup> subconjunctival injections  
 Transscleral diffusion from controlled release systems

**Non-invasive methods**

Topical administration on the eye

**Systemic administration**

Intravenous infusion and injection  
 Per oral

<sup>a</sup> The repetition is needed to accomplish long-term ocular treatment.

**Recent developments and future challenges in the field*****Implants***

The goal of the intraocular implant design is to provide prolonged activity with controlled drug release from the polymeric implant material. Intraocular administration of the implants always requires minor surgery. In general, they are placed intravitreally, at the pars plana of the eye (posterior to the lens and anterior to the retina) [14–16]. Although this is an invasive technique, the implants have the benefit of (1) by-passing the blood–ocular barriers to deliver constant therapeutic levels of drug directly to the site of action, (2) avoidance of the side effects associated with frequent systemic and intravitreal injections, and (3) smaller quantity of drug needed during the treatment. The ocular implants are classified as non-biodegradable and biodegradable devices [14]. Non-biodegradable implants can provide more accurate control of drug release and longer release periods than the biodegradable polymers do, but the non-biodegradable systems require surgical implant removal with the associated risks (Table 1). The ocular implants are summarized in Table 2.

Vitrasert<sup>®</sup> [14] and Retisert<sup>®</sup> [16] (Bausch & Lomb, USA) are clinically used non-biodegradable implants. Vitrasert<sup>®</sup> is the first implantable ganciclovir delivery device (approved by the FDA in 1996). The EVA and polyvinyl alcohol (PVA) polymers control the release of ganciclovir. It is effective in controlling the progression of CMV retinitis associated with AIDS for eight months, but occasional endophthalmitis and increased rate of retinal detachments have been associated with this implant [14].

Retisert<sup>®</sup> [16] is the first marketed fluocinolone acetonide implant for the treatment of chronic non-infectious uveitis of the posterior segment. PVA and silicone laminate govern the release of the corticosteroid during three years. Although the device is effective in controlling the uveitis, it also presents side effects like cataract and increased intraocular pressure.

Medidur<sup>®</sup> (Alimera Sciences, USA and pSivida Inc., USA) implant ([http://www.alimerasciences.com/medidur\\_overview.asp](http://www.alimerasciences.com/medidur_overview.asp)) can be inserted intravitreally as an injection, instead of a surgery. This tube-shaped device is in Phase III clinical trial for diabetic macular edema using fluocinolone acetonide. The device is very small (3 mm long and 0.37 mm of diameter) and its action lasts between 18 and 36 months after injection.

Kato *et al.* [17] carried out rabbit studies with scleral implant placed to the posterior pole. The device releases the drug, beta-methasone, constantly for at least three months without detectable drug concentration in the aqueous humor. Interestingly, the implant showed more effective delivery to the macular region than the intravitreal implants. The episcleral system is a promising means for the treatment of the retinal and choroidal diseases.

Surodex<sup>®</sup> [18] and Posurdex<sup>®</sup> (Allergan, USA) [19] are the biodegradable implants in clinical Phase III studies. They are nearly identical poly lactic-co-glycolic acid (PLGA) implants with different doses of dexamethasone (60 µg for Surodex<sup>®</sup> and 700 µg for Posurdex<sup>®</sup>). Surodex<sup>®</sup> was meant for the treatment of post-operative inflammation after filtering surgery on eyes with glaucoma placed underneath the scleral flap during the operation. Nevertheless, no further development of the implant is currently undertaken. Posurdex<sup>®</sup> is designed for the treatment of macular edema due to retinal vein occlusion, diabetic macular edema and uveitis by sustained release of dexamethasone over a month after intravitreal placement. In the future, Retisert<sup>®</sup> or Posurdex<sup>®</sup> may be chosen for the management of uveitis depending on the duration of the treatment needed.

Semi-solid bioerodible implant materials would enable delivery of soft implants with a needle and syringe. Heller [20] introduced such a material, poly(orthoester) IV, that shows long residence time after subconjunctival administration, an erosion-controlled drug release, and ocular biocompatibility. Depending on the ocular site of injection, the ocular lifetime of the drug ranges from five weeks to six months.

***Microspheres***

Another controlled release strategy is to encapsulate the drug in the microparticles [21–25] (1–1000 µm) or nanoparticles [21,26–31] (1–1000 nm). Biodegradable and biocompatible polymers, such as polylactide and PLGA, both approved by FDA, are typically used. These systems are usually given as intravitreal injection, a less invasive procedure than the surgical implantation. They provide sustained drug delivery for weeks or even months [12,21] (Box 1), allowing reduced number of injections. Furthermore, these carriers can be engineered to target certain cell types. The intravitreal injections of the particulate systems may cause vitreal clouding [12]. However, microparticles tend to sink to the lower part of the vitreal cavity, while nanoparticles are more susceptible to cause clouding in the vitreous (Table 1).

To date, some microsphere formulations have been in pre-clinical studies, but have not yet undergone clinical trials. The microspheres were administered subconjunctivally or periocularly to provide trans-scleral drug delivery instead of the invasive intravitreal administration. Microspheres of PKC412 [22], inhibitor of protein kinase C and receptors for vascular endothelial growth factor (VEGF), were used to treat the choroidal neovascularization. After a periocular injection, PKC412 penetrated the sclera and

TABLE 1

**Advantages and disadvantages of the current and potential drug delivery systems to treat ocular diseases**

|                                                                | <b>Advantages</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <b>Disadvantages</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|----------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Drops</b>                                                   | <ul style="list-style-type: none"> <li>- Easy to apply</li> <li>- The least invasive of the methods</li> <li>- Good patient acceptance</li> </ul>                                                                                                                                                                                                                                                                                                                                       | <ul style="list-style-type: none"> <li>- Poor ocular bioavailability</li> <li>- Sometimes short duration of action</li> <li>- Ineffective to treat diseases of the posterior segment of the eye</li> <li>- The high concentrations or frequent instillations may lead to ocular and systemic toxicity</li> <li>- Sometimes low patient compliance</li> </ul>                                                                                                                                                                                                                                                                                   |
| <b>Systemic administration</b>                                 | <ul style="list-style-type: none"> <li>- More effective to treat diseases of the posterior segment of the eye than drops</li> </ul>                                                                                                                                                                                                                                                                                                                                                     | <ul style="list-style-type: none"> <li>- Most of the administered drugs do not by-pass blood-ocular barriers</li> <li>- Side effects: systemic toxicity</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>Intravitreal, periocular and subconjunctival injections</b> | <ul style="list-style-type: none"> <li>- Improve drug absorption over systemically and topically delivered agents</li> <li>- More safety drug delivery to the posterior segment of the eye than systemic administration (no systemic toxicity)</li> <li>- Drug delivery to the target sites of the eye</li> </ul>                                                                                                                                                                       | <ul style="list-style-type: none"> <li>- Injections display first-order kinetics (this rapid rise may cause difficulties with toxicity, and drug efficacy can diminish as the drug concentration falls below the targeted range)</li> <li>- Injections have short half-life (few hours) and should be administered repeatedly</li> <li>- Side effects: repeated injections can cause pain, discomfort, IOP increases, intraocular bleeding, increased chances for infection, and the possibility of retinal detachment; the major complication for intravitreal injection is endophthalmitis</li> <li>- Poor acceptance by patients</li> </ul> |
| <b>Implants</b>                                                | <ul style="list-style-type: none"> <li>- An alternative to repeated injections because they increase half-life of the drug and may help to minimize peak plasma level; they might improve patient acceptance and compliance</li> <li>- Stabilization of the drug</li> <li>- The non-biodegradable implants are more controllable delivery profile and longer periods of drug release than biodegradable ones</li> <li>- The biodegradable implants do not need to be removed</li> </ul> | <ul style="list-style-type: none"> <li>- Side effects: the insertion of these devices is invasive and with associated ocular complications (retinal detachment and intravitreal hemorrhage for intravitreal implant)</li> <li>- The non-biodegradable require surgery to harvest the device once is depleted of the drug (risk of ocular complications)</li> <li>- The biodegradable implants have a final uncontrollable 'burst' in their drug release profile</li> </ul>                                                                                                                                                                     |
| <b>Microparticles, nanoparticles and liposomes</b>             | <ul style="list-style-type: none"> <li>- Stabilization of the drug</li> <li>- Increase half-life of drugs (the frequency of injections diminishes)</li> <li>- Decrease peak concentration resulting in decreasing the toxicity (micro and nanoparticles minimize 'BURST' in their drug delivery profile because the dose volume is limited)</li> <li>- Localized delivery of drug (RPE cells)</li> <li>- Improved patient compliance and convenience</li> </ul>                         | <ul style="list-style-type: none"> <li>- Side effects: risk associated with injections and vitreous clouding</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Cell encapsulation</b>                                      | <ul style="list-style-type: none"> <li>- Long-lasting and continuous expression of the given protein (avoiding repeated injections) without genetic alteration of the host tissues</li> <li>- Delivery directly to the target site (limiting toxicity)</li> <li>- Easy retrieval of the implant when desired (making the treatment reversible)</li> <li>- Improve patient compliance</li> </ul>                                                                                         | <ul style="list-style-type: none"> <li>- Side effects: invasive method with the complications related to the surgical insertion and removal</li> <li>- Patient acceptance to be seen</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Iontophoresis</b>                                           | <ul style="list-style-type: none"> <li>- Non-invasive method and easy to use</li> <li>- May combine with other drug delivery systems</li> <li>- Ability of modulate dosage (less risk of toxicity)</li> <li>- Good drug penetration to anterior and posterior segment of the eye</li> <li>- Good acceptance by patients</li> <li>- A broad applicability to deliver a broad range of drugs or genes to treat several ophthalmic diseases in the posterior segment of the eye</li> </ul> | <ul style="list-style-type: none"> <li>- No sustained half-life: requires repeated administrations</li> <li>- Side effects: mild pain in some cases, but no risk of infections or ulcerations</li> <li>- Risk of low patient compliance because the frequent administrations that may be needed</li> </ul>                                                                                                                                                                                                                                                                                                                                     |

significantly suppressed choroidal neovascularization. Gomes dos Santos *et al.* [23] designed PLGA microspheres for the sustained release of the nanosized anti-TGF $\beta$ 2 (transforming growth factor  $\beta$ 2) phosphorothioate antisense oligonucleotide complexes. A

subconjunctival injection prevented post-surgical fibrosis following trabeculectomy for 42 days. Since periocular and subconjunctival injections are less invasive than the intravitreal injections (Box 2), these studies demonstrate the potential of trans-scleral

TABLE 2

## Description of current and potential ophthalmic implants

| Registered name        | Active substance                    | Mode of administration                               | Implant size                                              | Marketing status |
|------------------------|-------------------------------------|------------------------------------------------------|-----------------------------------------------------------|------------------|
| Vitrasert <sup>®</sup> | Ganciclovir                         | Surgical implantation at the pars plana              | Millimetre size                                           | Clinical use     |
| Retisert <sup>®</sup>  | Fluocinolone acetonide              | Surgical implantation at the pars plana              | Tablet 3 mm × 2mm × 5 mm                                  | Clinical use     |
| Medidur <sup>®</sup>   | Fluocinolone acetonide              | Injected in the vitreous cavity                      | Cylindrical tube 3.5 mm in length and 0.37 mm in diameter | Phase III        |
| Posurdex <sup>®</sup>  | Dexamethasone                       | Injected or through small incision at the pars plana | Microsized implant                                        | Phase III        |
| Surodex <sup>®</sup>   | Dexamethasone                       | Placed underneath the scleral flap                   | Microsized implant                                        | Phase III        |
| NT-501                 | CNTF secreted by encapsulated cells | Surgical implantation at the pars plana              | Cylindrical tube 6 mm in length and 1 mm in diameter      | Phase II         |

route for prolonged drug delivery. Furthermore, Carrasquillo *et al.* [24] used microsphere system to release pegaptanib sodium (anti-VEGF aptamer) continuously at the scleral surface to provide prolonged delivery of the released aptamer. The study is relevant in the context of subconjunctival or peribulbar oligonucleotide delivery into the eye. Recently, a second drug delivery system for pegaptanib sodium was described [25]: intravitreal PLGA microspheres released aptamer over several weeks after injection.

#### Nanoparticulates for drug delivery

Many ocular nanoparticulate systems, like polymeric nanoparticles, liposomes, and micelles, are currently tested pre-clinically. Several systems are based on self-assembly of the surfactants, lipids, or polymers, while some nanoparticles require special processing.

#### Nanoparticles

Pre-clinical experiments have demonstrated nanoparticulates in RPE cells [26–28]. This is probably due to the phagocytic capacity of RPE, and indicates that nanoparticulates could be used to treat the retinal disorders. Bourges *et al.* [26] showed that the nanoparticles are retained within the RPE cells even four months after a single intravitreal injection. Thus the method may provide steady and continuous delivery of drugs or oligonucleotides.

Albumin nanoparticles are an interesting delivery system for intravitreal drug administration that has shown controlled drug release and degradation to safe products [29]. *In vivo* rat studies demonstrated their localization in the vitreous cavity and ciliary body for at least two weeks after a single intravitreal injection [29].

#### Micelles

Micelles are generated using amphiphilic surfactants or diblock polymers. Recently, a polyion complex micelle system that incorporates a dendritic phthalocyanine photosensitizer [32–34] was tested in rats for its efficacy in photodynamic therapy of choroidal neovascularization. The micellar system exhibited absorption at 650 nm, which is advantageous for the treatment of deep lesions. The formulation may prolong the retention in the blood circulation and achieve a selective accumulation in the choroidal neovascularized lesions, but these aspects require further development.

#### Liposomes

Liposomes are lipid vesicles of about 25–10 000 nm in diameter. There are various methods for preparation of liposomes with

different sizes, stability, and pharmacokinetics. Liposomes [35] are biocompatible, biodegradable, and they can be made of natural lipids. Hydrophilic and lipophilic drugs can be encapsulated to the lipid walls or the aqueous interior of the liposomes, respectively. The liposomes are taken up by phagocytic cells, like the RPE cells thus enabling intracellular drug delivery. Further, the liposomal surfaces can be modified to allow preferential binding, for example, to the endothelia of proliferating neovascular vessels. The limitations include potential intraocular clouding after the intravitreal injections. Liposome technology has been used to develop light-induced systems for the retinal diseases (for example Visudyne<sup>®</sup>, Novartis Pharmaceuticals, USA) [36,37].

#### Light-induced systems

Light-induced systems can be divided to two groups: light-activated drugs (i.e. photodynamic therapy) and light-activated drug delivery systems.

Verteporfin (Visudyne<sup>®</sup>) [36,37] is the only ocular liposomal drug currently in the clinical use. It works as photodynamic therapy to treat choroidal neovascularization and age-related macular degeneration. After intravenous infusion of Visudyne<sup>®</sup>, a non-thermal red laser is applied to the retina to activate verteporfin that causes local damage to neovascular endothelium, thus resulting in occlusion of the targeted vessels. Photodynamic therapy itself induces an increased local production of VEGF and potential reappearance of the choroidal neovessels [36]. Hence, the effect of Visudyne<sup>®</sup> is insufficient in some cases and the patients need repeated treatments.

Rostaporfin (Photrex<sup>®</sup>, Miravant Medical Technologies, USA) [37,38] is another liposomal photosensitizing agent that aims to treat age-related macular degeneration. Currently its FDA approval is pending. The frequency of the required treatments is significantly lower than Visudyne<sup>®</sup>.

A light-induced drug delivery system based on VP22, a structural protein of Herpes Simplex virus, was described recently [28]. The purified VP22 protein binds antisense oligonucleotide of human *c-ras* kinase. A fluorochrome is covalently linked to the protein or to the oligonucleotide. The spherical particles, vectosomes, migrated trans-retinally after an intravitreal injection into the rats. The carriers remained in the cytoplasm of various retinal cell types and trans-scleral illumination triggered the delivery of free oligonucleotides. The *c-ras* kinase plays a pivotal role in cell proliferation, resistance of apoptosis, and has influence on the VEGF

pathway. This is a promising method to treat neovascular tissue in the age-related macular degeneration and diabetic retinopathy.

Another light-triggered drug delivery system was described by Paasonen *et al.* [31]. They immobilized gold nanoparticles into the liposomes. Upon light exposure the liposomal contents were released, presumably owing to the heat transfer from the gold nanoparticles into the lipid bilayers, and subsequent increased leakiness of the lipid layer. The light-controlled drug delivery to the intraocular structures is of particular interest owing to the wide use of lasers in ophthalmology. Nevertheless, attention should be paid to the choice of the wavelength and energy of the laser to avoid retinal adverse reactions.

### Non-viral delivery systems for gene-based drugs

Gene-based drugs include gene therapy and other approaches that rely on the specific nucleotide sequences. The nucleotide sequence of DNA, RNA, or their modifications is used to induce gene expression (gene therapy), suppress translation of the target mRNA (siRNA, antisense oligonucleotides, ribozymes), or to bind to a specific protein target (aptamers) [39]. These approaches are applicable in the treatment of ocular diseases [40–42] and have some advantages compared with the conventional drugs. Firstly, compared with small molecule drug discovery it is easier to find the relevant nucleotide sequence of gene-based drug. Genes can express their protein products for prolonged periods and further control can be obtained by cell specific or inducible promoters [40].

Currently there are two ocular gene-based drugs in the clinical use. The first one was Vitravene<sup>®</sup>, fomivirsin sodium, intravitreal phosphorothioate oligonucleotide for the treatment of CMV infection in the AIDS patients [41]. The second one, pegaptanib sodium (Macugen<sup>®</sup>), is an anti-VEGF aptamer for the treatment of wet age-related macular degeneration [43,44]. The aptamer is conjugated to polyethylene glycol (PEG) to increase its half-life and stability in the vitreous. The same drug is currently in Phase II trials for the treatment of diabetic macular edema. In addition, two siRNA molecules (bevasiranib and Sirna-027) that modify the activity of VEGF and its receptor (VEGFR-1) have entered in the clinical trials (<http://www.gene.com/gene/index.jsp>, <http://www.sirna.com>). They are given as intravitreal injections.

In general, the gene-based medicines are hydrophilic large molecules with suboptimal delivery properties. Even though the compounds are administered in saline solution intravitreally, the delivery systems are useful in improving the intracellular access of these compounds and to improve their stability in biological fluids [41]. Thus, improvements in the efficacy and duration of action can be achieved. The delivery systems are classified into viral and non-viral vectors. Although viral vectors are more efficient in the delivery of genes, the non-viral systems have some advantages, such as the lack of immune response, the ease of formulation, and unlimited gene size [30]. In this drug delivery review we are describing only the non-viral delivery systems, because these technologies are applicable also in the delivery of aptamers, siRNA, and antisense compounds.

Some examples of pre-clinically investigated systems include microparticles [23–25], nanoparticles [26–31], and liposomes [45]. For example, a plasmid DNA compacted with PEG-substituted lysine peptides was used for non-viral gene transfer into the eye

[30]. Other systems include polyamidoamine dendrimer (treelike branched macromolecules) [46–48] and a cationic lipophilic peptide [49]. They are investigated as carriers to deliver antisense oligonucleotide of VEGF to treat choroidal neovascularization. One of the advantages of such systems is the prolonged drug activity after intravitreal injection. Bochot *et al.* [45] show that after intravitreal injection, the liposome formulation protected the oligonucleotide from the degradation and prolonged its vitreal residence time. The liposomes also reduced the distribution of oligonucleotide to non-target sites. Preferential uptake by the retinal cells opens up interesting treatment perspectives.

Cationic lipids and polymers are frequently used owing to binding and condensing of DNA and RNA to small particulates in the range of 100 nm. Despite their small size the nanoparticulate systems have limited diffusion in the tissues. For example, vitreous and neural retinas are substantial barriers that prohibit the spreading of the injected nanoparticulate systems after intravitreal administration [50,51]. This may be due to the steric hindrance and electrostatic interactions with ocular polyanions, such as hyaluronic acid and chondroitin sulfate.

Recently, the corneal epithelial barrier for protein drug absorption was overcome by transfecting the surface epithelial cells. Toropainen *et al.* [52] used eye drops that contained plasmid DNA condensed with cationic lipid composition DOTAP/DOPE. After topical ocular instillation the surface layer of the cornea and conjunctiva were transfected with marker gene encoding secreted alkaline phosphatase (SEAP). SEAP was secreted from the cells into the tear fluid and anterior chamber for several days. Similarly, the differentiated RPE can be transfected *in vitro* with liposomal nanoparticles (DOTAP/DOPE/protamine sulfate) to secrete the protein over prolonged periods of even two months [53]. These studies demonstrate the use of transfected ocular tissues as a platform for the secretion of therapeutic protein.

### Cell encapsulation

The principle of encapsulated cell technology (ECT) [54,55] is to entrap immunologically isolated cells with microcapsules or hollow fibers before their administration into the eye. This technology enables the controlled, continuous, and long-term delivery of therapeutic proteins directly to the back of the eye. This allows the implantation of genetically engineered cells that continuously produce the therapeutic protein at the site of implantation. Small 6 mm long ECT implants are placed through a small incision in the pars plana of the eye, yet outside of the visual axis. The implant is sutured in a manner that allows its retrieval when desired.

ECT product NT501 (Neurotech Inc., USA) [54] has just completed Phase I trials and is now entering Phase II. One eye in each of 10 patients with retinitis pigmentosa was implanted with the device for six months. During that time, the polymer implant that contains genetically modified human RPE cells secreted ciliary neurotrophic factor into the vitreous of the patients' eyes. The device proved to be well tolerated by patients and showed an improvement in visual acuity scores of some patients. ECT could potentially serve as a delivery system for chronic ophthalmic diseases without effective therapies (e.g. neuroprotection in glaucoma, anti-angiogenesis in choroidal neovascularization, anti-inflammatory factors for uveitis) [55]. However, its long-term safety and efficacy remains to be seen.

### Iontophoresis

Iontophoresis is a non-invasive method of transferring ionized drugs through membranes with low electrical current [56,57]. The drugs are moved across the membranes by two mechanisms: migration and electro-osmosis.

Ocular iontophoresis is classified into trans-corneal, corneoscleral or trans-scleral iontophoresis [56], the latter being the most interesting option. The sclera has larger surface area than the cornea (about 17 cm<sup>2</sup> versus 1.3 cm<sup>2</sup>) high degree of hydration, low number of cells, and it is permeable to large molecular weight compounds [4]. Trans-scleral delivery allows drug transfer to the posterior segment.

A few ocular iontophoresis systems have been investigated recently: OcuPhor<sup>®</sup> (Iomed Inc., USA) [58], Eyegate II Delivery System<sup>®</sup> (EyeGate Pharma, USA) [59], and Visulex<sup>®</sup> (Aciont Inc., USA) [60–63]. These devices avoid the adverse effects that were frequently observed in the past studies with higher electrical current densities [58,59]. These devices are also easier to use than the older iontophoretic systems. Eyegate II Delivery System<sup>®</sup> [59] is the first one that was used in the patients. On the basis of the first experiences it is effective, easy to use, and well tolerated.

The iontophoretic technique is less invasive than the intraocular injections, but the duration of the drug action is less prolonged than with the controlled release systems. Unlike transdermal iontophoresis the mechanisms of the trans-scleral iontophoresis have not been investigated in detail. However, the properties of the sclera (hydration, leakiness, low electrical resistance) make the iontophoretic delivery feasible at low electric currents or voltages. This has been shown in the case of corticoids, immunosuppressive agents, and oligonucleotides [56,59–64]. The drug loss by the conjunctival and choroidal blood flow was decreased by co-administration of a vasoconstrictor (oxymethazoline) [63]. The efficacy and patient acceptance in the broad clinical applications are not yet known.

### Gelifying systems

Another strategy to obtain an ocular sustained drug delivery system is to use various phase changing polymers. These materials can be delivered in a liquid form, as an eye drop or intraocular injection. After instillation the polymer undergoes a phase change and forms a semi-solid or solid matrix that releases the drug over prolonged period. The phase transition can be induced by the

change in the temperature, ion concentration, or pH. There are several polymers that have such properties.

For topical ocular use, the gel forming solutions, such as Timoptic-XE<sup>®</sup> (Merck and Co. Inc., USA) ([http://www.merck.com/product/usa/pi\\_circulars/t/timoptic/timoptic\\_xe\\_pi.pdf](http://www.merck.com/product/usa/pi_circulars/t/timoptic/timoptic_xe_pi.pdf)), Pilogel<sup>®</sup> (Alcon, Inc., Switzerland) (<http://home.intekom.com/pharm/alcon/pilogel.html>) and Azasite<sup>®</sup> (Insite Vision, USA) ([http://www.insitevision.com/marketed\\_products](http://www.insitevision.com/marketed_products)) are already in the clinical use. For example, Timoptic-XE<sup>®</sup> contains gellrite (purified anionic heteropolysaccharide from gellan gum), whereas poly(acrylic acid) is incorporated in the Pilogel<sup>®</sup> eye drops. These materials enhance the drug retention relative to the conventional eye drops and lead to increased drug absorption into the eye and reduced dosing frequency. However, the duration of drug activity can be increased by hours, not by days or weeks. It has been assumed that the gelifying systems could improve out-patient compliance, but this was not the case in a recent study described by Kahook [65].

Clearly, a new breakthrough is needed before topical ocular gelifying delivery systems can provide truly prolonged drug action or drug delivery to the posterior segment. Subconjunctival and parabolbar gelifying injections are interesting alternatives for the posterior segment drug delivery, but their final therapeutic value must be further investigated.

### Conclusions

Ocular drug delivery has become an increasingly important field of research. Advances in the ocular drug delivery systems research are expected to provide new tools for the treatment of the eye diseases with the new therapeutic modalities, like antibodies, aptamers, and siRNA. These delivery methods should provide prolonged action, less invasive administration, higher efficacy, and improved safety. The injectable or implantable prolonged acting systems should guarantee patient adherence to the drug therapy. Development of sustained and non-invasive posterior segment delivery systems for the self-administration by the out-patients is still an unrealistic technological challenge. Major technological breakthroughs are needed before that goal becomes reality. There are several scientific and technological advances that are driving the progress in this field. Especially the advances in nanotechnology and biomaterials science may provide new smart technologies to augment ophthalmic drug delivery.

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# Expert Opinion

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## Periocular routes for retinal drug delivery

Swita Raghava, Makena Hammond & Uday B Kompella<sup>†</sup>

Despite numerous scientific efforts, delivery of therapeutic amounts of a drug to the retina remains a challenge. This challenge is compounded if chronic therapy is desired. The inability or inefficiency of topical and systemic routes for retinal delivery of existing drugs is now widely accepted. Although the intravitreal route offers high local concentrations in the vitreous and, hence, retina, these advantages are offset by side effects, such as cataracts, endophthalmitis and retinal detachment, following repeated intravitreal injections, or intravitreal placement of sustained-release implants. As discussed in this review, periocular routes, including subconjunctival, sub-tenon, retrobulbar, peribulbar and posterior juxtасcleral routes, potentially offer a more promising alternative for enhanced drug delivery to the retina compared with topical and systemic routes. Periocular routes exploit the permeability of sclera for retinal drug delivery, and they are particularly useful for administering sustained-release systems of potent drugs. This review discusses the various periocular routes with respect to their anatomical location, pharmacokinetics, safety and mechanisms of drug delivery. In the coming years, several innovations in absorption enhancement, drug delivery systems and drug administration devices are anticipated for improving retinal drug delivery via periocular routes.

**Keywords:** peribulbar, pharmacokinetics, retina, retrobulbar, subconjunctival, sub-tenon, sustained release

### 1. Introduction

Drug delivery to the posterior segment of the eye is useful in treating various disorders, including degenerative, vascular and proliferative disorders (Table 1). The retina is the primary target for most of these disorders. Delivery of therapeutic concentrations of drugs to the retina continues to remain a challenge for pharmaceutical scientists because of the anatomical and physiological barriers associated with this tissue [1,2]. The challenges are compounded if chronic therapy is required, as is the case with diabetic retinopathy and age-related macular degeneration. Topical instillation of drug solution into the inferior fornix of the conjunctiva is most often used for ocular administration, and this route has been successful in treating diseases afflicting the anterior segment of the eye. For topically administered medications, the cornea and conjunctiva are the primary barriers for ocular drug entry. These barriers, in conjunction with nasolacrimal drainage of administered drops, drug metabolism, protein binding, lens barrier and long diffusional path lengths, result in poor drug delivery to the retina following topical administration. Systemically administered therapeutic agents reach the retina to a limited extent due to the presence of blood–ocular barriers, which include the blood–aqueous and blood–retinal barriers. The blood–aqueous barrier is formed by the non-pigmented layer of the ciliary epithelium and the endothelium of the iris vessels. The blood–retinal barriers include the retinal pigment epithelium and the endothelium of the retinal vessels. Due to these barriers and low

**Table 1. Disorders afflicting the posterior segment of the eye.**

| Classification         | Examples                                                                                                               | Target tissue                       |
|------------------------|------------------------------------------------------------------------------------------------------------------------|-------------------------------------|
| Degenerative diseases  | Age-related macular degeneration, retinitis pigmentosa                                                                 | Retina                              |
| Vascular diseases      | Diabetic retinopathy, retinal vein or arterial occlusion, retinopathy of prematurity, age-related macular degeneration | Retina                              |
| Inflammatory diseases  | Uveitis                                                                                                                | Uveal tissues, sclera, iris, retina |
| Proliferative diseases | Proliferative vitreoretinopathy                                                                                        | Vitreous and retina                 |
| Infectious diseases    | Endophthalmitis                                                                                                        | Vitreous and/or retina              |
| Others                 | Glaucoma, optic neuritis                                                                                               | Optic nerve                         |

cardiac output to the retina [3], attainment of therapeutic effect in the retina requires high systemic doses, which can produce harmful side effects because most drugs intended for the eye were originally developed for systemic use [4,5].

To improve the retinal delivery of drugs, various local modes of administration, including intracameral, intravitreal and periocular routes, have been assessed. Intracameral injection refers to injection of drug solution in the anterior chamber of the eye. Up to 100 µl volume can be injected by this route. Intracameral injections are used in cataract surgery and for the management of diseases afflicting the anterior segment. This route of administration fails to deliver significant concentrations of drugs to the posterior segment [6].

Since the first report on intravitreal injections in 1944, this mode of administration has found wide clinical application for treating vitreoretinal disorders [7]. Intravitreal injections can provide high drug concentrations to the neural retina. However, bolus intravitreal injections result in high local concentrations of drugs, which can potentially cause retinal toxicity, as is the case with gentamicin [8]. In addition, repeated intravitreal injections can lead to retinal detachment [9]. The half-lives of representative drugs in the vitreous following intravitreal administration are summarised in **Table 2** [10-13]. It is noteworthy that the elimination half-lives of drugs increase with molecular weight in the vitreous. On the other hand, in the plasma, peptide and protein drugs exhibit short elimination half-lives [14]. Due to this unique vitreal clearance property, macromolecules such as vascular endothelial growth factor (VEGF) aptamer and VEGF antibody fragments are under development for intravitreal administration. However, such drugs still require repeated intravitreal administrations in treating chronic disorders, which might exacerbate the risks.

Periocular routes, which for the purpose of this article include subconjunctival, sub-tenon, retrobulbar, peribulbar and posterior juxtасcleral, offer alternative approaches for delivering drugs to the retina (**Figure 1**). If a drug is administered by these routes, it can be delivered to the sclera, choroid, retinal pigment epithelium, neural retina and vitreous, in that order, depending on source concentration and the barrier properties of these and other intermittent layers between the site of administration and the target site. As these routes are showing promise for retinal delivery of some drugs, the following discussion provides a

description of the methods of administration, pharmacokinetics, mechanisms of delivery, sustained-release systems and pharmacodynamics for periocularly administered drugs.

## 2. Periocular routes

### 2.1 Subconjunctival

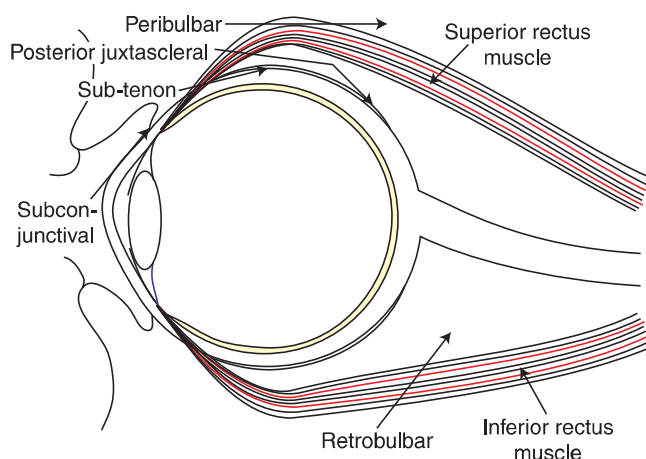
Subconjunctival injection implies injection of the drug solution underneath the conjunctiva. The conjunctiva is a thin continuous membrane lining the eye beginning from the eyelids to the corneoscleral junction. A needle of up to 25 – 30 gauge and 30 mm long, and a volume of up to 0.5 ml may be used for this particular method of administration. During injection, the bevelled edge of the needle is made to face the sclera and is slid under the bulbar conjunctiva, which is loosely attached to the sclera  $\geq 3$  mm beyond the limbus, until a fold appears [15]. This route has been previously shown to be effective in delivering drugs to both the anterior and posterior segments of the eye.

### 2.2 Sub-tenon

Although sub-tenon injections were reported as early as 1956, they were not extensively used until 1990 [16]. Sub-tenon administration usually implies injection of drugs into the tenon's capsule around the upper portion of the eye and into the belly of the superior rectus muscle [15]. The tenon's capsule is a fibrous membrane that envelopes the globe from the margin of the cornea to the optic nerve [17]. The sub-tenon space is a virtual cavity bound by the tenon's capsule and the sclera, and is divided into anterior and posterior segments at the insertions of the extraocular muscles and their associated fasciae [18]. While injecting drugs, the patient is directed to look downward as the upper lid is retracted [15]. Subsequently, a 2.5 cm long, blunt-tipped cannula needle is passed into the tenon's capsule at the temporal edge of the superior rectus muscle after a surgical dissection into the sub-tenon's space is made. The injection is directed posteromedially, and up to 4 ml of drug formulation is injected around the muscle belly behind the equator [19]. Although subconjunctival haemorrhaging may be a complication, sub-tenon injection is a widely used technique for anaesthesia during ocular surgery, due to the fact that sharp needle complications can be avoided with the cannula approach. The conventional technique for

**Table 2. Vitreous humor half-lives of drugs administered intravitreally.**

| Drug administered           | Molecular weight | Species | Half-life (h) | Reference |
|-----------------------------|------------------|---------|---------------|-----------|
| ISIS 2922 (oligonucleotide) | 7122.16          | Rabbit  | 62            | [10]      |
| Octreotide acetate          | 1019.3           | Rabbit  | 16            | [11]      |
| Dexamethasone               | 392.47           | Rabbit  | 3.48          | [12]      |
| Ceftizoxime                 | 405.38           | Rabbit  | 5.7           | [13]      |

**Figure 1. Schematic representation of periorbital routes of administration.**

posterior sub-tenon injection involves the use of a sharp-tipped 26-gauge 5/8 inch needle that must be inserted up to its hub to obtain adequate placement of the drug into the posterior sub-tenon space.

### 2.3 Retrobulbar

Retrobulbar injection refers to the injection in the conical compartment within the confines of the four rectus muscles and their intermuscular septa [16]. Injection of a drug formulation is made within the muscle cone behind the globe of the eye [20]. This injection is usually performed with a blunt 25- or 27-gauge needle. Although sharp needles cause less pain due to injection, using a needle tip with less cutting ability reduces inadvertent injury to the eye [21]. The entry site for retrobulbar injection begins at the inferotemporal orbital margin with the eye in the primary gaze position, and the needle is aimed at the lower edge of the superior orbital fissure [22]. Typically, the needle is directed 45° from the sagittal plane and 10° superiorly. After insertion of ~ 3 mm beyond the posterior surface of the globe, an injection of up to 5 ml may be made. The globe is ~ 25 mm in diameter. Therefore, the needle should not be directed behind the globe until this depth has been reached from the most anterior surface of the cornea. This type of injection places the optic nerve at risk for trauma including a subarachnoid injection. To avoid optic nerve injury, the needle is kept in the temporal half of the orbit and should penetrate no further than 1.5 cm behind the globe [21].

With retrobulbar injection, higher local concentrations may be achieved for anaesthesia or akinesia of the globe during surgery, and there is little to no influence on intraocular pressure.

### 2.4 Peribulbar

Peribulbar injection was popularised in 1986 as an alternative to avoid the complications experienced with retrobulbar method [19]. Peribulbar injection indicates an injection made at the location external to the confines of the four rectus muscles and their intramuscular septa [16]. With this method, unlike the retrobulbar method, the muscle cone is never entered [20]. Peribulbar injection can be performed in two ways – that is, injection at the inferotemporal position after a slight cephaloposterior trajectory and injection at the supro-nasal position just below and medial to the supratrochlear notch. Inferior injections are given at the junction of the outer third and inner two-thirds of the lower orbital rim [19]. The needle is directed away from the eye and toward the floor of the orbit, with the eye in primary gaze position. Superior injections can be given either nasally or temporally toward the roof of the orbit. However, temporal administration is preferable due to the fact that the regions encountered are less vascular. Depth of the needle is controlled by observing the needle-hub junction reaching the plane of the iris. A 25-gauge, 1.25 inch needle is used and directed just beyond the equator of the globe. It has been reported that depending on the compliance and speed of injection, up to 8 – 10 ml of anaesthetic may be given in a periconal fashion. To avoid the risk of globe perforation, care should be taken to ensure that the needle is placed away from the globe. The peribulbar route is less effective than the retrobulbar route in anesthetising the globe. However, it is a safer mode of administration.

### 2.5 Posterior juxtascleral

This is a unique delivery approach developed by Alcon Laboratories Ltd, which uses a blunt-tipped, curved cannula for delivering the drug formulation in direct contact with the outer surface of the sclera without puncturing the eyeball [23]. This delivery route is being used by Alcon to deliver a depot formulation of anecortave acetate (Retaane®), being investigated to treat age-related macular degeneration patients. This approach allows placement of the depot near and above the macula, allowing efficient and prolonged drug delivery to the macular region. For the drug administration, the patient is placed supine, the suspended medication is drawn into the

syringe, and a specially designed 56° cannula is then placed on the syringe [23]. After applying povidone-iodine 5% to the periocular skin and cul-de-sac, a lid speculum is inserted. After topical anaesthesia, to expose the sclera, a 1 – 1.5 mm incision is made in the superotemporal quadrant, midway between the superior and lateral rectus muscles, through the conjunctiva and tenon's capsule, 8 mm posterior to the limbus. When sclera is visualised, the curved portion of the cannula is inserted, keeping the cannula tip in constant direct apposition to the scleral surface. Once the cannula is fully inserted without resistance, pressure is applied along the sides and top of the cannula with a pair of sterile cotton swabs to prevent any reflux, and 0.5 ml of the medication is injected slowly. The cannula is withdrawn while maintaining gentle pressure using the cotton swabs. Following this procedure, the lid speculum is removed, topical antibiotic is applied, and the eye is patched lightly.

## 2.6 Safety of periocular injections [16-18]

As periocular routes are most widely used for ocular anaesthesia, safety information is readily available for the administration of anaesthetics by these routes. Because of the proximity of the injection site to the nerves and muscles that need paralyzing prior to surgery, retrobulbar injections are the most efficient among periocular routes in anaesthetising the globe. However, these injections are associated with the highest number of complications. The complications include retrobulbar haemorrhage, globe perforation and respiratory arrest as a result of brainstem anaesthesia, with their incidence being 1.7, 0.75 and 0.3%, respectively. Peribulbar anaesthesia is safer, with a 0.0008% incidence of globe perforations and no occurrence of retrobulbar haemorrhage or respiratory arrest. Compared with retrobulbar and peribulbar injections, which use sharp needles, the sub-tenon approach employing a cannula is emerging as a safer alternative. For this reason, the Royal Colleges of Ophthalmologists and Anaesthetists have endorsed sub-tenon block as a procedure in which an anaesthetist need not be present, if a sharp-needle block is not being employed. Swelling of conjunctiva or chemosis and subconjunctival haemorrhage are complications associated with sub-tenon injections, with an incidence rate of 39.4 and 32 – 56%, respectively.

The risks associated with retrobulbar and peribulbar injections can be further minimised through the latest technological advances such as real-time tomography reflection of sonographic images [24]. In sonography, the operator must look away from the patient in order to see the sonographic screen and, therefore, must rely on a displaced sense of hand-eye coordination. This problem can be overcome by exploring methods for viewing the sonographic image, patient, instrument, and operator's hand in one environment. It has been observed that with the use of Sonic Flashlight, the globe, optic nerve and retrobulbar space can be visualised at their expected visual locations relative to the external anatomy. Chang [24] reported that on insertion of the needle, the

needle can be clearly seen passing the region inferior to the globe and into the retrobulbar space, while easily avoiding surrounding structures. With the same technique, the needle puncturing the globe is also clearly visualised. Sonography can potentially be employed to avoid the risks associated with other periocular injections. Unlike eye drops, the disseminated use of periocular routes for drug delivery may be limited by access to well-equipped medical care facilities, especially in the developing world.

## 3. Pharmacokinetics of periocularly administered drugs

An understanding of drug absorption, distribution and elimination (pharmacokinetics) is indispensable in identifying a therapeutic regimen and designing a delivery system [25]. However, there are very few ocular pharmacokinetic studies conducted in humans, because there is no safe way of continuously sampling intraocular tissues or fluids without causing pain or injury. Therefore, drug development for the eye relies heavily on preclinical pharmacokinetic studies. The usefulness of animal models in predicting human ocular pharmacokinetics can be improved by taking into account the anatomical and physiological dissimilarities between the eyes of various species. Ocular preclinical pharmacokinetic studies have been helpful in [25]: determining the best route of administration for entry into the eye, as well as accumulation at the site of action; validating the minimum effective concentrations in various tissues from different routes of administration; determining the elimination half-life, which can serve as a guide to the selection of dosing regimens for further study; and estimating the safety of various drugs by determining their accumulation in the relevant tissues.

In order to obtain valid results with drug delivery and pharmacokinetic studies, the investigators should establish validated assays and tissue isolation procedures. Ideally, the tissue isolation procedures should ensure lack of cross-contamination between various tissue layers, and eliminate drug diffusion between tissues post-isolation and prior to analysis. For determining drug levels in the retina, isolated neural retina is desired, as opposed to retina-choroid preparations.

### 3.1 Drug delivery to the posterior segment from eye drops

Interest is growing in determining whether a drug administered as an eye drop reaches the posterior segment of the eye to any significant levels. Although the literature is supportive of drug delivery to the posterior segment of the eye from topical drops, the concentrations achieved are a minute fraction of the concentration in the dosing solution [26]. However, if the drug is highly potent and there is appreciable drug accumulation in the target tissue, pharmacological effects may be seen in the posterior segment of the eye that can be attributed to the eye drops. A study in pigmented rabbits concluded that topical instillation of a 0.03% solution of iganidipine, a  $\text{Ca}^{2+}$

antagonist, delivers drug to the ipsilateral posterior retina or retrobulbar periocular space by local penetration at concentrations sufficient to act as a  $\text{Ca}^{2+}$  antagonist [27]. It was observed that 20-day instillation of iganidipine 0.03% b.i.d., but not of betaxolol (0.5%), significantly suppressed constriction of the retinal arteries in the ipsilateral eye induced by intravenous injection of endothelin-1. Intravenous injection of iganidipine at a dose of 30  $\mu\text{g/kg}$  significantly suppressed intravenous endothelin-1-induced constriction of the retinal artery to a similar degree as 20-day instillation of iganidipine 0.03% b.i.d. After a single instillation of 0.09% iganidipine, the equivalent concentration of iganidipine in the ipsilateral retrobulbar periocular space estimated from autoradiography was  $\sim 3.9 \times 10^{-8}\text{M}$  between 15 min and 1 h after instillation, consistently higher than the levels in the untreated contralateral eyes by  $\sim 3 \times 10^{-8}\text{M}$ .

Nepafenac, a non-steroidal anti-inflammatory agent, has been shown to prevent the mitogen-induced pan-retinal oedema following topical ocular application in rabbits [28]. Topical application of 0.5% nepafenac produced 65% reduction in retinal oedema, which correlated with 62% inhibition of blood-retinal barrier breakdown. Topical nepafenac also inhibited ocular neovascularisation in three murine models [29]. Mice treated with 0.1 or 0.5% nepafenac exhibited significantly less choroid neovascularisation and significantly less ischaemia-induced retinal neovascularisation compared with vehicle-treated mice.

A recent study indicated that insulin accumulates in the retina and optic nerve following topical application [30].

The above findings indicating the delivery of iganidipine, nepafenac and insulin are consistent with the non-corneal or conjunctival route of drug delivery reported by Ahmed and Patton [31]. Thus, it is not surprising that drugs administered next to the sclera can enter the intraocular tissues.

### 3.2 Rationale for the use of periocular routes for retinal drug delivery

Even though only a small fraction of the concentration of topically administered eye drops (estimated by Maurice at 1/1500 for lipophilic metipranolol and 1/150,000 for hydrophilic fluorescein) reaches the aqueous humor [32], several hydrophilic and lipophilic drugs are administered routinely as drops for treating glaucoma. Some of these topical drops are claimed to have effects in the posterior segment. It is fair in the authors' opinion to assume that some potent drugs will be useful in delivering therapeutic drug levels to the posterior segment of the eye when they are administered periocularly. Periocular routes, as discussed below, generally deliver greater drug levels to the posterior segment of the eye compared with the topical or systemic modes of administration. A large dilution of the dosing solution at target site [26] does not mean that the fraction delivered to the posterior segment of the eye is of a similar magnitude, because various distribution parameters lead to spontaneous dilution of the drug in different tissues. This is analogous to administrations

of low-molecular-weight drugs by the intramuscular route, wherein the peak plasma concentrations attained would be a very small fraction of the concentration of the drug in the dosage form, but the fraction absorbed could be nearly complete. The fraction of the dose absorbed into the posterior segment of the eye from the periocular routes is expected to be higher than is feasible with topical administration and generally even following systemic modes of administration. However, the actual fraction absorbed following periocular administration will be low due to drug loss into the blood, as suggested by Lee and Robinson [33,34].

Even low bioavailability of a drug should not deter a drug from development, especially if it is potent and has a good safety profile at doses required for exerting the therapeutic effect. Lessons can be learned from drugs administered by other routes. One such example is naferelin, a peptide drug with activity on the pituitary gonadal axis, which allows its use in the treatment of precocious puberty and endometriosis. This peptide is available as a nasal spray at a concentration of 2 mg/ml for the treatment of endometriosis and precocious puberty. The average peak concentration was 0.6 ng/ml in the serum following a single nasal spray of 100  $\mu\text{l}$  naferelin solution in adult women, and this was 2.2 ng/ml in children with precocious puberty following the administration of two nasal sprays [35]. Thus, there is at least 1,000,000 times dilution of the dosing solution in serum, and this dilution would be even greater at the target tissues. The estimated serum bioavailability of this drug from the nasal cavity is 2.8% in healthy female volunteers [36]. This is only one example among several commercially available drugs, in which not the target:dosage form drug concentration ratio, but the effect, becomes the driving force for drug product development. In other words, potent yet safe drug molecules will find multiple applications by the periocular routes.

### 3.3 Pioneering work in periocular pharmacokinetics

Several investigators have assessed the pharmacokinetics of periocularly administered drugs. Key contributors to this area included M Barza, J Robinson and D Maurice, among others. The following summarises some key findings in this area.

Barza, through meticulously designed studies, determined the pharmacokinetics of drugs, primarily antibiotics intended for treating intraocular infections, with the target for delivery being the vitreous [13]. He demonstrated that drugs can enter the vitreous following subconjunctival, sub-tenon and retrobulbar administrations. He also suggested that the drug entry is more localised within the eye to the region of administration with subconjunctival administration and more uniformly distributed to the intraocular tissues with retrobulbar administrations. His investigations, along with those of Maurice early on indicated that the injection of the drug subconjunctivally in the superior quadrant of the eye results in greater drug levels in the anterior segment of the eye compared with an injection in the inferior quadrant [37,38]. However, these two modes of administration did not result in any significant differences in the vitreous drug

**Table 3. Delivery of dexamethasone to the subretinal fluid following administration by various routes.**

|                          | Subconjunctival | Peribulbar                | Oral                      | Reference |
|--------------------------|-----------------|---------------------------|---------------------------|-----------|
| C <sub>max</sub> (ng/ml) | 359 (80.2)      | 82.2 (17.6) <sup>‡</sup>  | 12.3 (1.61) <sup>‡</sup>  | [43]      |
| T <sub>max</sub> (h)     | 2.45 (0.166)    | 3.01 (0.134) <sup>‡</sup> | 5.06 (0.433) <sup>‡</sup> |           |
| Dose (mg)*               | 2.5             | 5                         | 7.5                       |           |
| Number of patients       | 49              | 50                        | 49                        |           |

\*Dose is expressed as the weight of dexamethasone disodium phosphate administered. <sup>‡</sup>The values in the parenthesis represent standard error.

levels. These findings can be explained on the basis that when the drug is injected in the superior quadrant, it directly drains into the tear film over the cornea, exposing greater concentrations of the drug to the cornea compared with an injection made in the inferior quadrant. The similar quantities in the vitreous may be because the pathways followed to the vitreous (penetration across sclera and systemic pathway) are similar for both modes of administration. Investigations of Wine [39] and Maurice and Ota [37] demonstrated that the backward drainage of solution along the needle track, as well as the diffusion across the conjunctiva into the tear film, contribute to high drug levels attained in the anterior segment of the eye following subconjunctival injection. The contribution of high drug levels to the anterior segment following subconjunctival injection are unequivocal, and injections are recommended in several clinical situations [40]. However, if the same therapeutic goals can be accomplished with eye drops, the drops are preferred.

To understand the relative contribution of the drug entering the anterior chamber to the vitreous level after subconjunctival injection, Lee and Robinson [6] carried out a study in New Zealand albino rabbits. <sup>14</sup>C-mannitol was injected subconjunctivally, and <sup>14</sup>C-mannitol and <sup>14</sup>C-inulin were injected intracamerally. The aqueous and vitreous levels were determined at selected time points. The authors found that movement of the drug from the aqueous chamber backwards to the vitreous after subconjunctival injection contributes minimally to drug levels in the vitreous. Although a minute quantity of the drug can enter the vitreous via this pathway, this pathway can be practically neglected as a potential pathway for drug delivery to the posterior segment of the eye after subconjunctival injection. Although fraction absorbed has been estimated to be low for subconjunctivally administered drugs [33], systematic studies need to be performed to quantify the fraction of the dose absorbed into the tissues of the posterior segment. Whereas such an assessment would be straightforward in the vitreous, similar measures in the retina would be more difficult.

Based on the work of Barza, which demonstrated that subconjunctival injections result in less than the desired concentrations of antibiotics in the vitreous, sufficient caution should be exercised in choosing the type of drug to be delivered to the posterior segment via periocular routes, especially if the vitreous is the intended target. In the case of cephalosporins, even though 3 – 13 mg/l concentrations were attained in the vitreous following single subconjunctival

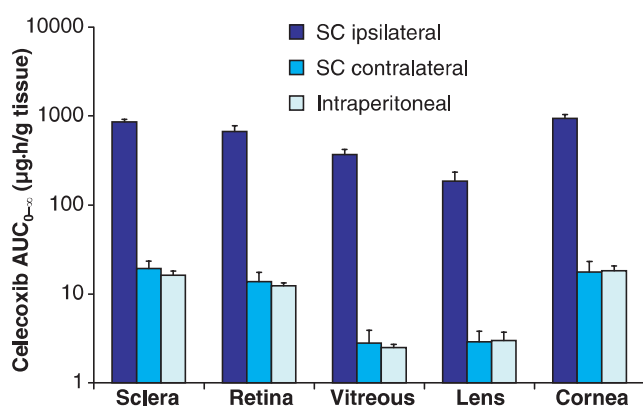
injection in rabbits, they were deemed to be insufficient [13]. It appears that more potent molecules should be chosen for this mode of administration.

In summary, pharmacokinetic literature comparing the various periocular routes for their effectiveness in delivering drugs to the tissues of the posterior segment is sparse. Systematic studies have been performed for antibiotics. Subconjunctivally administered drugs can leak back along the needle track or diffuse across conjunctiva to reach the tissues of the anterior segment. A small fraction of the dose administered periocularly reaches the tissues of the posterior segment including the vitreous. The levels achieved in the vitreous may not be effective for antibiotics such as cephalosporins assessed by Barza. Thus, more potent drugs should be chosen if vitreal drug delivery is intended. In addition, the drug loss to the blood circulation should be minimised by employing innovative approaches in order to enhance the fraction of the dose absorbed into the posterior segment. The various periocular routes are likely to result in different pharmacokinetic profiles for a given drug. Although Barza and group addressed this to an extent for antibiotics, it deserves renewed attention due to the availability of superior analytical techniques.

### 3.4 Periocular routes deliver drug to the vitreous in humans

From their study to determine the dexamethasone concentration in aqueous, vitreous and serum of phakic patients after a subconjunctival injection of dexamethasone disodium phosphate, Weijtens [41] concluded that subconjunctival injection is more effective compared with peribulbar and oral administrations for delivering dexamethasone into the posterior segment of the eye. These levels are higher than those obtained in the vitreous following topical instillation in humans [42]. The authors also observed considerable systemic absorption following subconjunctival injection. The dose of dexamethasone injected subconjunctivally was 2.5 mg. The estimated maximum dexamethasone concentration was 858 ng/ml at 2.5 h after injection in the aqueous, and 72.5 ng/ml at 3 h in the vitreous. In serum, a mean maximum concentration of 32.4 ng/ml was measured at ~ 30 min after injection.

A comparison of subretinal fluid concentration of dexamethasone attained following subconjunctival, peribulbar and oral administration of dexamethasone disodium phosphate to patients with a rhegmatogenous retinal



**Figure 2. Local delivery is responsible for higher ocular tissue availability of celecoxib following subconjunctival administration.** Celecoxib suspension was administered SC to one eye at a dose of 3 mg/rat, and drug levels were estimated in the tissues from the dosed (ipsilateral) eye as well as the undosed (contralateral) eye. In addition, drug suspension was administered intraperitoneally at a dose of 3 mg and the drug levels were estimated in various ocular tissues. The area under the tissue concentration versus time plot ( $AUC_{0-\infty}$ ) is expressed as mean  $\pm$  s.d. for  $n = 4$  for subconjunctival injection and  $n = 6$  for intraperitoneal injection [44].

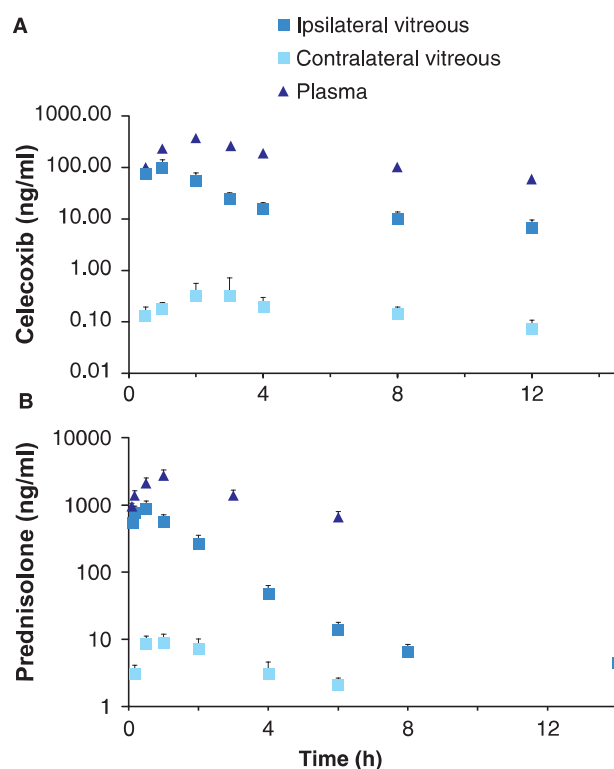
AUC: Area under the curve; SC: Subconjunctivally.

detachment revealed that subconjunctival injection is more effective in delivering dexamethasone disodium phosphate into the subretinal fluid (Table 3) compared with peribulbar injection or oral administration [43]. Corrected for dose, the maximum dexamethasone concentration after subconjunctival injection and peribulbar injection were, respectively, 120 and 13 times greater than oral administration.

Thus, periocular administration delivers more dexamethasone phosphate to the posterior segment compared with systemic or topical administration in humans.

### 3.5 Local retinal delivery is predominant following periocular administration

Substantially higher drug levels in the retina can be attained following subconjunctival administration as compared with the systemic route. A study towards this end in the authors' laboratory quantified the relative retinal bioavailability of celecoxib from the subconjunctival route compared with the intraperitoneal route in rats (Figure 2) [44]. For the subconjunctivally dosed (ipsilateral) eye, the area under the curve ( $AUC_{0-\infty}$ ) ratios between subconjunctival and intraperitoneal groups were  $0.8 \pm 0.1$ ,  $53.1 \pm 3.5$ ,  $54.3 \pm 8.4$ ,  $144.5 \pm 21$ ,  $60.7 \pm 15.6$  and  $51.6 \pm 5.7$ , for plasma, sclera, retina, vitreous, lens and cornea, respectively. For the contralateral ocular tissues, the  $AUC_{0-\infty}$  ratios were  $1.2 \pm 0.2$ ,  $1.1 \pm 0.3$ ,  $1.1 \pm 0.4$ ,  $1 \pm 0.3$  and  $1.2 \pm 0.3$ , in the sclera, retina, vitreous, lens and cornea, respectively, between the subconjunctival and the intraperitoneal groups. Thus, the drug delivery to the retina and other ocular tissues is superior to systemic mode of administration



**Figure 3. Subconjunctival route for retinal delivery of drugs in rats and rabbits.** (A) Celecoxib levels in the vitreous and plasma of Sprague–Dawley rats following subconjunctival injection of a 50  $\mu$ l suspension containing 3 mg drug. The data are expressed as mean  $\pm$  s.d. for  $n = 4$  [44]. (B) Prednisolone levels in various tissues after subconjunctival injection of a 50  $\mu$ l solution containing prednisolone at 1 mg/kg dose in New Zealand white rabbits. The data are expressed as mean  $\pm$  s.e.m. for  $n = 3$  [45].

by  $> 50$ -fold for celecoxib. Assuming that the drug AUCs in contralateral eye were equal to the systemic pathway contribution to AUCs in the ipsilateral eye, the percentage contribution of local pathways as opposed to systemic circulation for celecoxib delivery to the ipsilateral eye tissues was estimated to be  $\geq 98\%$ . Thus, the contribution of systemic recirculation pathway to the drug levels in the intraocular tissues following subconjunctival injection is negligible for celecoxib in rats. Figure 3A shows drug levels in the rat vitreous following subconjunctival administration of 3 mg of celecoxib as a suspension in 0.5% carboxymethylcellulose [44]. The injection volume was 50  $\mu$ l. For comparative purposes, drug levels in the vitreous and serum for prednisolone administered subconjunctivally in a rabbit model are shown in Figure 3B [45]. It can be seen that the two models have provided similar information about the two drugs – that is, vitreal drug levels following the subconjunctival route of administration are contributed primarily by local delivery or diffusion across local barriers as opposed to delivery via the systemic recirculation pathway. In both animal models, significant vitreous:plasma/serum AUC ratios were observed for the drugs in the ipsilateral eyes.

Table 4. Properties of human sclera.

| Property                                          | Value                                                                                                                                           | Reference |
|---------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Computerised tracings                             | 16.3 ± 1.8 cm <sup>2</sup>                                                                                                                      | [51]      |
| Volume displacement                               | 17.0 ± 0.5 cm <sup>2</sup>                                                                                                                      |           |
| At limbus                                         | 0.53 ± 0.14 mm                                                                                                                                  | [52]      |
| Near the equator                                  | 0.39 ± 0.17 mm                                                                                                                                  |           |
| Near the optic nerve                              | 0.9 – 1.0 mm                                                                                                                                    |           |
| Structural composition                            | Collagen fibres (up to 75% dry weight), water (68%), mucopolysaccharides (0.7 – 0.9% dry weight), proteoglycans, elastic fibres and fibroblasts |           |
| Highest molecular weight known to permeate sclera | 70,000                                                                                                                                          |           |

Thus, in the rat and rabbit models, periocularly administered drug reaches the tissues of the posterior segment primarily via local delivery as opposed to systemic pathway.

### 3.6 Periocular routes for macromolecule delivery

Macromolecule delivery to the intraocular tissues can be achieved following periocular administration [46]. The serum concentration from a retrobulbar injection of IFN- $\alpha_{2a}$  were reported to be < 1% of the choroidal concentration, and it was suggested that the retrobulbar route can be used to deliver IFN- $\alpha_{2a}$  for the treatment of choroidal neovascularisation. Ambati demonstrated that the retinal delivery of a macromolecule (fluorescein isothiocyanate [FITC]-labelled IgG) can be sustained from the subconjunctival space in a rabbit model [47]. An osmotic pump was used to deliver IgG across the sclera of pigmented rabbits, and IgG levels were measured in various tissues over 28 days. They observed that the drug was localised more to the choroid proximal to the injection site compared with the distal choroid. Interestingly, the macromolecule persisted in the choroid and retina for a long period, as indicated by the elimination half-life of the macromolecule, which was of the order of days from choroid and the retina following the cessation of drug delivery. Maurice [48] demonstrated that the removal of macromolecules from the subretinal space is slow, with 80% of FITC-dextran 150S being detectable at the end of 3 days following subretinal injection in rabbits with experimental non-rhegmatogenous retinal detachments. Carboxyfluorescein, on the other hand, was not detectable in the subretinal space after 8 h. Although trace quantities of FITC-dextran 150S were detected in the vitreous of this model, significant quantities of FITC-dextran 70S and carboxyfluorescein were detectable in the vitreous.

Using the then available limited means, as early as 1978, Maurice has obtained evidence that whereas small ions can disappear from the subconjunctival space within a few minutes, macromolecules are retained for prolonged periods [37]. Following subconjunctival administration of immunoglobulin, another group observed peak levels of the protein in the cornea on day 6, suggesting prolonged retention of the

molecule in the subconjunctival space [49]. If the conjunctiva is less permeable to macromolecules compared with sclera, it may benefit trans-scleral macromolecule delivery following periocular administration.

Some macromolecules administered by the periocular route may not reach the neural retina due to the presence of the retinal pigment epithelium. Gelbach [50] observed that periocular administration of an adenoviral vector encoding pigment epithelium-derived factor (PEDF) resulted in high levels of PEDF in the retinal pigment epithelium (RPE) and choroid, but not in the retina. Periocular gene delivery systems express protein in the periocular region, leading to protein secretion followed by diffusion across sclera into the tissues of the posterior segment.

Thus, macromolecules permeate the sclera and they exhibit prolonged residence in the subconjunctival and subretinal spaces. In addition, they are known to be cleared slowly from the vitreous [32]. The RPE layer is rate-limiting in the delivery of macromolecules to the neural retina. Thus, retinal delivery of macromolecules poses unique challenges and opportunities.

## 4. Mechanisms of trans-scleral drug delivery

Trans-scleral delivery is less invasive to the eye compared with intravitreal injection, and it provides local delivery of high-molecular-weight compounds to the posterior segment. Human sclera is hypocellular and has a large surface area, both of which facilitate diffusion (Table 4) [51,52]. The primary route for solute transport through the sclera is by passive diffusion through an aqueous pathway. Figure 4 [53-57] summarises the permeability coefficients for several solutes across human sclera. Henry Edelhauser contributed substantially in understanding various aspects of trans-scleral drug delivery, including scleral permeability, scleral surface area, scleral thickness and the usefulness of depot systems in trans-scleral drug delivery [52].

Intraocular distribution of a 70 kDa tetramethylrhodamine-dextran (TMR-D) after subconjunctival injection was studied in mice [58] to determine the mechanisms of drug delivery.

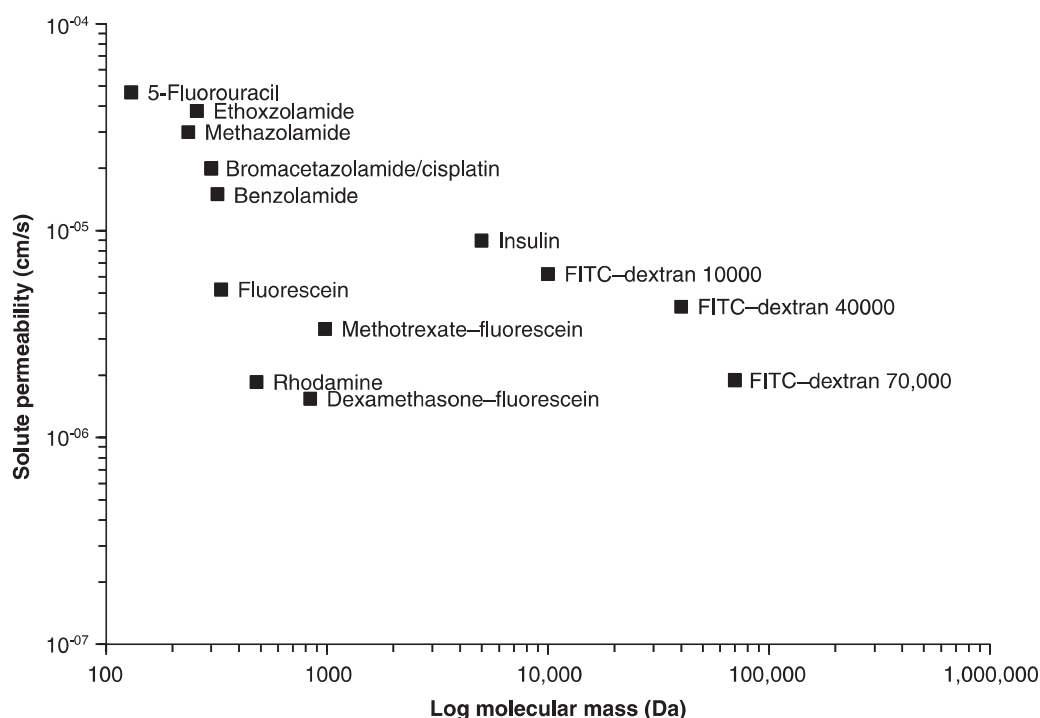


Figure 4. Permeabilities of various solutes across human sclera [53-57].

TMR-D readily diffused trans-sclerally and dispersed throughout a large portion of the sclera, uvea and cornea. Shortly after the injection, homogenous fluorescence was observed in the sclera and choroid on the same meridian as that of the injection site. This fluorescence gradually decreased in intensity with distance from the injection site. The intensity of scleral and choroidal fluorescence adjacent to the optic nerve reached a maximum at 1 h and then decreased slowly, with half-lives of ~ 16 and 100 h, respectively. Visible fluorescence was maintained for at least 72 h in the sclera, choroid, iris and cornea. Based on this, it was concluded that macromolecular 70 kDa dextran can be delivered to the mouse retina and uveal tissues following subconjunctival injection through trans-scleral diffusion, local hematogenous spread, and possibly movement through the uveo-scleral outflow pathway.

The various major pathways that a drug can traverse following periocular administrations are summarised in Figure 5. There are several barriers that the drug can encounter after diffusing across the sclera. After crossing the sclera, the tissues encountered by the drug include choroid, retinal pigment epithelium, outer limiting membrane, neural retina, inner limiting membrane, and the vitreous in that order. Depending on the target site, the drug has to cross one or more of the intermittent layers. Several of these can pose significant barriers for retinal drug delivery, with choroidal blood flow and retinal pigment epithelial barriers being the most significant. The vascular supply in the choroid is likely to clear

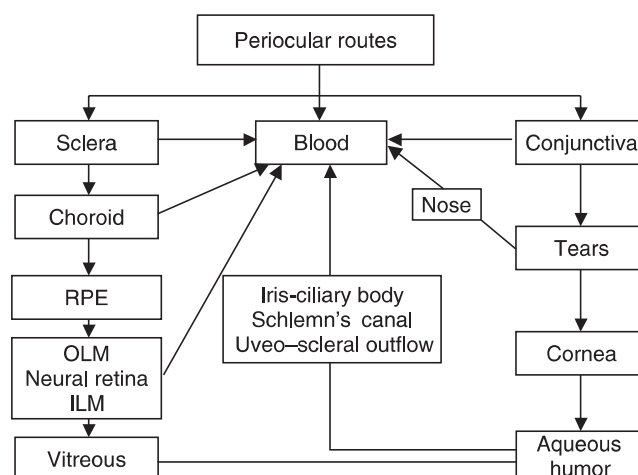
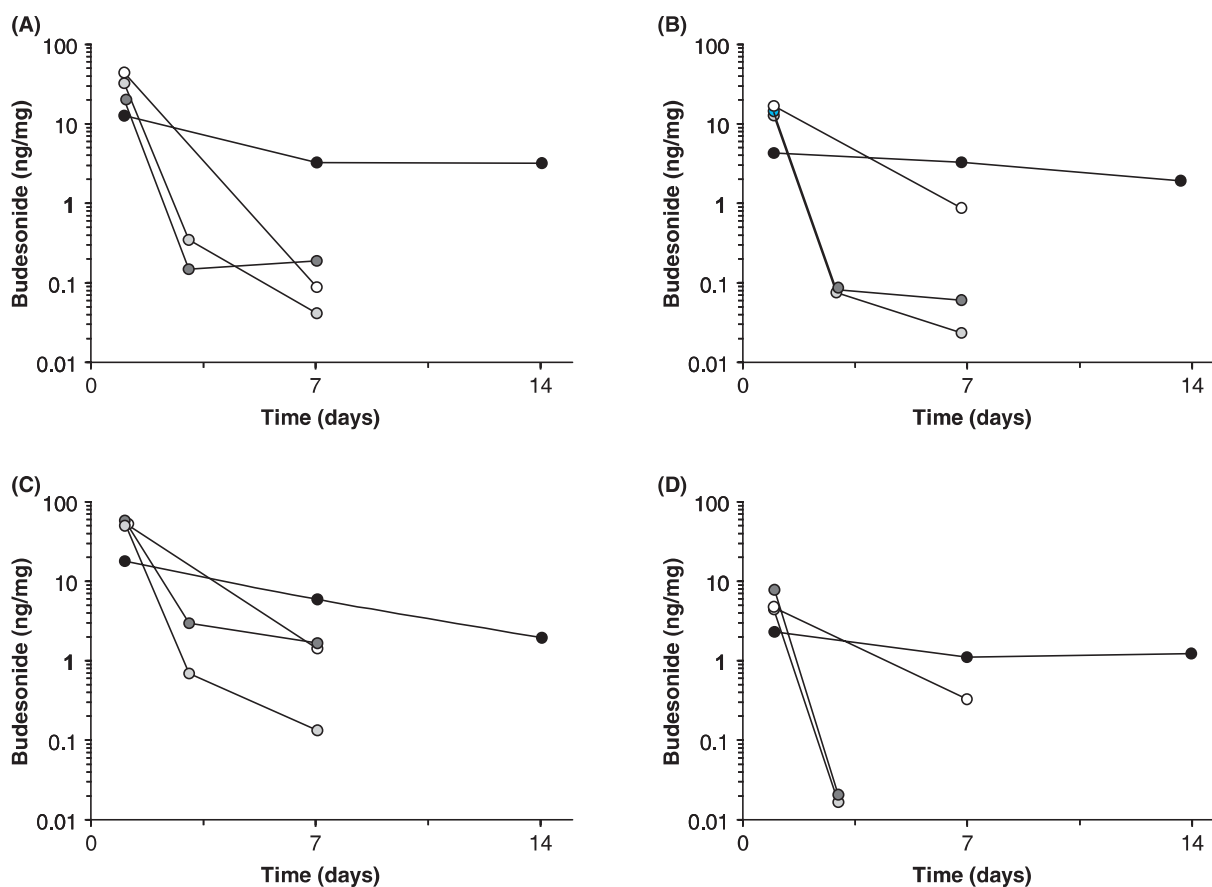


Figure 5. Pathways for intraocular and systemic delivery of drugs following periocular administration.

ILM: Inner limiting membrane; OLM: Outer limiting membrane; RPE: Retinal pigment epithelium.

the drug rapidly. Early on, the investigations of Maurice indicated that application of local pressure to the subconjunctival site of drug administration can elevate the drug delivery to the posterior segment, by reducing local choroidal blood flow [59]. With the application of pressure at the site of subconjunctival administration in rabbits at 10 min post-injection for 25 min,



**Figure 6. Budesonide nano- and microparticles sustained ocular tissue levels of budesonide after subconjunctival administration in rats.** Budesonide was administered in the eyes of rats, either in the form of a solution (50 or 75 µg to one eye; white and light grey circles, respectively), nanoparticles (50 µg to one eye; dark grey circles), or microparticles (75 µg to one eye; black circles), and drug levels were estimated in (A) retina, (B) vitreous, (C) cornea and (D) lens. Data are expressed as the mean ± s.d. of results in four experiments. Data are shown for the ipsilateral eye. Drug levels were below detection limits in the contralateral eye. Budesonide levels were below detection limits on day 14 in the solution and nanoparticle groups. Reproduced with permission from KOMPELLA UB, BANDINI, AYALASOMAYAJULA SP: Subconjunctival nano- and microparticles sustain retinal delivery of budesonide, a corticosteroid capable of inhibiting VEGF expression. (2003) 44(3):1192-1201, Copyright © Association for Research in Vision and Ophthalmology [62].

the peak vitreal concentrations of fluorescein and carboxyfluorescein were elevated by 19- and 4-fold, respectively. Thus, a reduction in choroidal blood flow can substantially enhance the drug delivery to the posterior segment. In addition, the clearance of fluorescein, but not carboxyfluorescein, was reduced by threefold following application of pressure at the subconjunctival site. The retinal pigment epithelium, the outer blood–retinal barrier, is another significant barrier that a drug has to surpass following periocular administration prior to entering the neural retina. The RPE layer has tight intercellular junctions that restrict the movement of solutes, especially macromolecules. The entry of FITC–dextran 70 and 150S from the subretinal space into the vitreous was significantly elevated following disruption of the RPE layer with intravenous sodium iodate in an experimental rhegmatogenous retinal detachment rabbit model [48], consistent with the

rate-limiting nature of RPE for solute permeability. If macromolecules cross the RPE layer due to special transport mechanisms and/or high concentration gradients, their movement into the neural retina may be hindered by the inner limiting membrane [50]. If the drug target is in the choroid or the retinal pigment epithelium, those sites would be more readily accessible compared with the neural retina or the vitreous humor following periocular injections. If a drug is lipophilic, or if it binds to the pigment in the choroid or retinal pigment epithelium, only a fraction of the drug present in the tissue will be entering the vitreous humor. Entry of macromolecules into the vitreous from the neural retina is also restricted by the outer limiting membrane. Due to the presence of these multiple tissue layers, it is not surprising that drugs were detected in low concentrations in the vitreous following periocular administrations.

In addition to the aforementioned delivery of the drug to the tissues of the posterior segment, drug could permeate the conjunctiva, especially following subconjunctival administration, and enter the tear film and tissues of the anterior segment (Figure 5). At various locations, including the site of administration, episclera, conjunctiva, choroid and retina, drug could be lost to the blood circulation. Minimisation of these losses would better retain the drug in the tissues of the posterior segment.

Thus, human sclera is highly permeable, which allows the delivery of even macromolecules to the intraocular tissues. The underlying choroid circulation and retinal pigment epithelium, which are likely to be the major rate-limiting steps in the drug delivery to the neural retina and vitreous, deserve further investigations with respect to their role in trans-scleral drug delivery. In addition, as drug loss to the circulation at the site of administration limits the drug absorption into the intraocular tissues, the mechanisms of drug loss at each periorbital site and approaches to overcome these need to be investigated.

## 5. Sustained release systems for periorbital delivery

Prolonging the retention of the drug in the periorbital regions can provide sustained drug levels and enhanced drug absorption into the intraocular tissues. Sasaki [60] demonstrated that periorbital injections containing 3% carboxymethylcellulose (CMC) as a viscous vehicle decreased the absorption rate constant of timololol, a model  $\beta$ -blocker, from the injection site to the systemic circulation compared with the buffer solution [61]. Compared with the results after periorbital injections with buffer solution, CMC increased the AUCs in the vitreous body 3.1-fold with retrobulbar injection and 1.4-fold with palpebral conjunctival injection, respectively. Thus, it is likely that various adjuvants in the formulations administered periorbitally can influence drug delivery.

Chronic ocular disorders can most efficiently be managed by maintaining the drug concentrations within the therapeutic window at the target site in the eye and reducing the frequency of administrations. To address this aspect of ocular drug delivery, a large number of sustained and controlled release drug delivery systems, namely implants, gels, microparticles and nanoparticles, are being investigated. Implants can release drug either in one direction (towards sclera) or from all sides. Implants can be placed either episclerally or intrasclerally after thinning the sclera. Gels can be based on several polymeric materials including biopolymers such as fibrin. Similar to the intravitreal route, a long-term trans-scleral delivery device may be clinically feasible because the human eye is tolerant of some materials overlying the sclera, such as scleral buckles used in treating retinal detachment, even for years.

Subconjunctival injection of drug-loaded microparticles and nanoparticles can also be employed for sustained retinal drug delivery [62]. The authors have previously shown that

subconjunctivally administered budesonide–polylactide (budesonide–PLA) nano- and microparticles sustain retinal drug delivery. Ocular tissue levels of budesonide were compared after a single subconjunctival injection of either budesonide solution (containing 50 or 75  $\mu\text{g}$  of budesonide), budesonide–PLA nanoparticles (containing 50  $\mu\text{g}$  of budesonide) or budesonide–PLA microparticles (containing 75  $\mu\text{g}$  of budesonide), and drug levels were estimated up to 14 days (Figure 6) [62]. With budesonide–PLA nanoparticles, the retinal levels of budesonide were 2- and 9-times higher than the budesonide solution-treated groups at the end of 3 and 7 days, respectively. The nanoparticles group had a 5.5-times higher vitreous budesonide concentration compared with the budesonide solution-treated group at the end of day 7. At the end of days 3 and 7, the corneal levels of budesonide with the nanoparticle formulation were 4- and 27-times higher than that of the budesonide solution-treated group. On comparison of subconjunctival injection of budesonide–PLA microparticles (75  $\mu\text{g}$  budesonide dose) to subconjunctival injection of budesonide solution (75  $\mu\text{g}$  budesonide dose), it was found that on day 1, drug levels in the solution group were 3.5-, 5.5-, 3- and 2-times higher in the retina, vitreous, cornea and lens, respectively, when compared with microparticle group ( $p < 0.05$  for all tissues). On day 7, drug levels in the microparticle group were 37-, 5-, 4.2- and 3.4-times higher in the retina, vitreous, cornea and lens, respectively, compared with the solution group. Similarly on day 14, drug levels in the microparticle group were higher compared with the solution group, wherein the drug levels were  $3.5 \pm 1.14$ ,  $0.8 \pm 0.21$ ,  $1.9 \pm 0.3$  and  $1.2 \pm 0.25$  ng/mg tissue weight in retina, vitreous, cornea and lens, respectively [62]. Microparticles better sustained drug delivery compared with the nanoparticles.

For sustained retinal drug delivery, it is hypothesised that those particles that are retained in the periorbital space would be more appropriate. This is because if the particles are not cleared, they can release the drug over a prolonged period for subsequent delivery to the tissues of the posterior segment. The periorbital retention of particles depends on their size. Microparticles (2  $\mu\text{m}$ ) are almost completely retained in the periorbital space even at 2 months post-administration, whereas nanoparticles (20 nm) completely disappear from the periorbital space [63]. Neither microparticles nor nanoparticles of the above dimensions enter the intraocular tissues to a significant extent from the periorbital space. Future studies should elucidate the mechanisms of clearance of particulate systems from the periorbital space.

Saishin [64] investigated the sustained local delivery of PKC412, a kinase inhibitor, following periorbital injection of poly(lactide-co-glycolide) microspheres containing 25 or 50% PKC412 in a porcine model. The levels of PKC412 attained after 20 days following periorbital injection of 25% microspheres were 1.2 ng/ml vitreous, 0.5 ng/retina, and 2 ng/choroid, respectively, whereas those with 50% microspheres were 35 ng/ml vitreous, 19 ng/retina and

155 ng/choroid, respectively. In plasma, the levels of PKC412 20 days post-injection were undetectable.

Feasibility of drug delivery to the posterior segment of the rabbit eye with an episcleral implant capable of delivering the drug in one direction towards the sclera was evaluated for betamethasone [65]. Such a system minimises the drug loss to the conjunctival circulation. The implant showed a zero-order release profile both and for 4 weeks. Betamethasone concentrations in the retina choroid after implantation were maintained above concentrations effective for suppressing inflammatory reactions for at least 4 weeks. The drug concentration was greater in the posterior half of retina-choroid than in the vitreous. In the vitreous, the maximum concentration was 13 ng/g at 2 weeks after implantation.

In brief, several sustained-release drug delivery systems including gels, particulate systems and implants have been shown to sustain the drug delivery to the retina following periocular administration. As repeated periocular administrations would be inconvenient, drug delivery systems capable of sustaining drug delivery for a few months to years are desirable.

## 6. Pharmacodynamics

Posterior sub-tenon's steroid injections (PSTSIs) are a standard drug delivery method used for the treatment of chronic uveitis of the posterior segment [66]. A retrospective study done in a uveitis clinic to analyse the indications, efficacy and complications of PSTSIs in the treatment of chronic uveitis concluded that PSTSIs are very effective in restoring visual acuity in chronic uveitis of the posterior segment, without systemic complications, but at the expense of intraocular hypertension. An intravenous cannula made of polytetrafluoroethylene has been used to inject corticosteroids safely into the posterior sub-tenon space [67].

Studies have shown that posterior sub-tenon's injection of corticosteroids significantly decreases cystoid macular oedema [68]. The first study reported in the UK to investigate the efficacy and safety of posterior sub-tenon triamcinolone acetonide injection demonstrated that these injections significantly decrease cystoid macular oedema with a corresponding increase in visual acuity in patients with uveitis. Systemic immunosuppression may be reduced or discontinued with the avoidance of associated systemic side effects, and the technique has a high level of patient acceptability. A retrospective study performed to compare the effectiveness of retrobulbar and posterior sub-tenon's injection of corticosteroids for the treatment of post-cataract cystoid macular oedema that was refractory to topical medications found that both treatment methods resulted in significant improvement in visual acuity. There was no significant difference between the improvement in cystoid macular oedema achieved after retrobulbar or posterior sub-tenon's corticosteroid injections [69].

In a masked, randomised, placebo-controlled study, anecortave acetate depot suspension administered posterior juxtasclerally was assessed for its benefits in patients with subfoveal choroid neovascularisation (CNV) [23]. It was observed that at month 12, a 15 mg dose of the drug administered at 6-month intervals was superior to the placebo in maintaining vision, preventing severe vision loss and inhibiting subfoveal CNV lesion growth.

Ambati demonstrated that an osmotic pump containing mouse antihuman intercellular adhesion molecule (ICAM)-1 mAb exerts pharmacological effects in the retina and choroid following subconjunctival administration [47]. VEGF-induced leucostasis in the retina and choroid, as measured by myeloperoxidase activity, was inhibited by the delivery of anti-ICAM-1 mAb. Myeloperoxidase activity in the choroid of the eye treated with anti-ICAM-1 mAb (2 mg/ml delivered at 8 µl/h) was 80% less than in the eye receiving an equal rate of delivery of an isotype control antibody (n = 5). Inhibition of myeloperoxidase activity in the retina was 70% (n = 5).

Ayalasomayajula and Kompella demonstrated that celecoxib-containing poly(lactide-co-glycolide) microparticles sustain the retinal delivery of celecoxib and inhibit oxidative stress in a diabetic rat model [70]. Saishin [64] demonstrated the effectiveness of periocularly injected poly(lactide-co-glycolide) microspheres containing 25 or 50% PKC412 in a porcine model. The areas of choroid neovascularisation at Bruch's membrane rupture sites were significantly smaller in eyes that received a periocular injection of microspheres containing 25 or 50% PKC412 than those in eyes injected with control microspheres. These data suggested that trans-scleral sustained delivery of agents is a viable approach for treatment of choroidal diseases.

Periocularly-injected adenoviral vector encoding VEGF receptor-1, sFlt-1 (ADsFlt-1.10), has been shown to be effective in a mouse model for choroid neovascularisation [50]. Periocular injection of ADsFlt-1.10 markedly suppressed choroidal neovascularisation at rupture sites in Bruch's membrane and also caused significant reduction in VEGF-induced breakdown of the blood-retinal barrier, but failed to significantly inhibit ischaemia-induced retinal neovascularisation. The lack of effect on retinal neovascularisation is possibly because the secreted protein did not cross the retinal pigment epithelium to reach the neural retina.

Thus, there is growing evidence indicating the effectiveness of periocularly-administered drugs in alleviating uveitis, cystoid macular oedema, choroid neovascularisation and diabetic retinal changes.

## 7. Future challenges

As the work of Lee and Robinson [6,33,34] has indicated, the fraction of drug absorbed can be reduced by the rapid loss of the drug from the periocular sites into the systemic circulation, prior to drug entry into the intraocular tissues via the sclera. To overcome this, systems that deliver the drug unidirectionally

towards the sclera while eliminating the drug entry into the systemic circulation would be beneficial. Kim [71], using a non-invasive magnetic resonance imaging study, reported that from an episcleral implant, 30-fold greater vitreous solute levels can be achieved at the end of 4 h in a rabbit used post-mortem compared with a live rabbit. This finding suggests that the blood circulation in various layers of the eye limits trans-scleral drug delivery. In future, approaches need to be developed to overcome this limitation. Alternatively, a breach in the retinal pigment epithelial barrier during the course of the study following euthanasia can explain these results. The retinal pigment epithelial barrier is likely to be more formidable than any currently available cell culture models indicate. To further improve the penetration of the drug into intraocular tissues, various absorption enhancement approaches can be assessed for their safety and efficacy [72]. Because the periocular injections should be made in a way that does not perforate the globe, development of better administration devices would be helpful. As several ophthalmic industries have expertise in drug and device development, this may come naturally to these organisations. Traditionally, periocularly-administered drugs are mainly off-label uses of drug products developed for other routes of administration. As there are several chronic disorders that afflict the posterior segment of the eye, pharmaceutical industries should devote more resources to developing products primarily intended for administration by these routes.

## 8. Conclusions

Periocular routes of administration include subconjunctival, sub-tenon, peribulbar, retrobulbar and posterior juxtасcleral modes. Drugs administered by these routes can be transported across sclera to the tissues of the posterior segment. The choice of these routes depends on the intended purpose and target tissues. There is limited pharmacokinetic and pharmacodynamic data with these routes. Current literature indicates that the drug delivery to the posterior segment is generally superior by this route compared with topical and systemic routes. Potent drug molecules can potentially be delivered by this approach for their effects in various tissues of the posterior segment. As repeated injections by these routes

would be inconvenient and increase the risk potential, sustained release systems are being developed for treating various chronic disorders of the posterior segment.

## 9. Expert opinion

The retina is a relatively inaccessible tissue to the blood circulation, not unlike the brain tissue. Drugs intended for effects in the brain are routinely administered orally. Such is not the case for the retina, as drug discovery and development efforts typically do not focus on the design of orally administered drugs that are safe and effective in the retina. Instead, drugs developed for other systemic diseases are usually assessed for their retinal effectiveness. In the absence of eye-specific drug design, retinal delivery can be enhanced using multiple approaches including the periocular routes of administration. In general, periocular routes can deliver the drug better to the retina compared with the systemic or topical modes of administration. The concerns associated with periocular routes include the fraction of drug absorbed and safety. Administration by skilled operator along with the use of technologies such as sonography can reduce the risks associated with the periocular modes of administration. Even with existing safety issues for periocular routes, these routes are potentially much safer than the intravitreal mode of administration, which is the current route of choice for providing high drug levels to the retina. Each route has its place in drug delivery and the choice of route should be based on the disease target (e.g., vitreous versus choroid) and the nature of the disease (e.g., acute versus chronic). If acute therapy is desired, intravitreal injections are viable. For chronic therapy, intravitreal implants or periocular sustained release systems that maintain drug levels for months to several years would be suitable. Repeated administrations are likely to be more amenable and safe with periocular routes.

## Acknowledgements

This work was supported by NIH grants DK064172, DK064172-02S1 and EY013842. The authors wish to thank UNMC for awarding graduate fellowship to S Raghava, and Drs C Camras and E Margalit of UNMC for a critical review of this manuscript.

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