ejpmr, 2022,9(6), 141-144

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

TOPICAL OCULAR PHARMACOLOGY- AN ANCIENT INDIAN VIEW

Dr. Pranav Bhagwat*

India.

***Corresponding Author: Dr. Pranav Bhagwat**

India.

Article Received on 02/04/2022 **Article Revised on 22/04/2022** **Article Accepted on 12/05/2022**

ABSTRACT

Topical ocular drug delivery has immense challenges due to corneal and precorneal factors. Ayurveda, an age-old science of medicine, had devised effective solution towards increasing drug availability in ocular tissues. This article discusses the barriers and strategies towards ocular drug absorption, visualises effects of fluid dynamics, clever pharmacological preparations, and pulsatile therapies towards achieving higher concentrations of medicines as described by *Sushrutasamhita*, a treatise on Ayurveda.

KEYWORDS: topical ocular pharmacotherapeutics-*kriyakalpa*- drug residence- viscosity-sheer stress-transscleral absorption.

INTRODUCTION

The science of pharmacology is concerned with the effects of drugs on the function of living tissues (Greek= Pharmakos= drug, logos=study). Since modern medicine relies heavily on the use of drug as a principal tool for the treatment & prevention of the diseases it is imperative for the clinician to have a basic understanding of the pharmacology. Ayurveda, an ancient medical science from India, also gives utmost importance to drugs, second only to clinician, in the treatment of diseases.

Many drugs, both topical and systemic are used in the treatment of eye diseases. However, the eye presents a particular challenge for drug delivery due to various barrier mechanisms that have evolved to protect the delicate ocular tissues from noxious substances. Ayurveda, has particularly given specific pharmacological preparations & drug delivery systems, named as '*KRIYAKALPA* (therapeutic preparations)*'*, to overcome these barriers. The *kriyakalpas* are further subdivided into *Tarpana, Putapaka, Aschyotana, Anjana, Bidalaka, Pindi*.[1]

Ocular pharmacokinetics

Pharmacokinetics is the study of drug absorption, distribution, metabolism, and excretion. A fundamental concept in pharmacokinetics is drug clearance, that is, elimination of drugs from the body. [(2)] The bioavailability of the drug, which refers to the fraction of the drug available at the site of action, in case of the ophthalmic preparations largely depends upon its absorption, in contrast to the orally administered drugs which are altered by stomach, liver or gut wall. The topical administrations also undergo systemic absorption across the nasal mucosa and escape first pass metabolism; hence, they are more effective and have a greater possibility of systematic effects.

The major differences of understanding ocular therapeutics between western pharmacology and ayurveda are described in Table no. 1.

Table 1:

Western medicine	Ayurveda
Systemic absorption dangerous, non-essential, wastage of medicines	Systemic absorption useful, helping *Agni*, (digestive power) increasing therapeutic use of medicines.
Nasal absorption dangerous	Nasal absorption encouraged.
Ocular Irritation is avoided	Ocular irritation welcomed for certain diseases.
Consideration of corneal absorption and concentration in aqueous plays a major role in designs.	Trans-Scleral, conjunctival, and indirect routes are also important.
Do not consider role of vitreous.	Have taken help from vortex movements in vitreous.

Topical administration

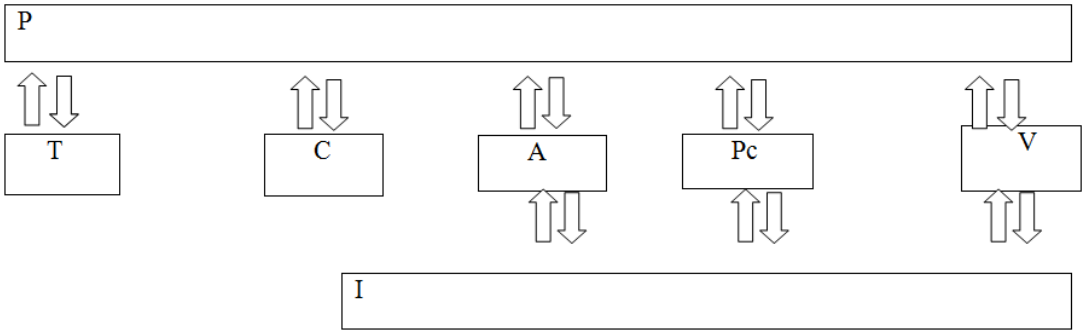
Topical administration of the drugs is the method of choice for most of eye diseases. One of the main problems with this route is the rapid & extensive pre corneal loss. A single drop from a conventional dropper bottle weighs about 40-50 micro litre and which is far more than the holding capacity of conjunctival sac & following a blink only about 10 micro-l of the drug remains.

Following pre-corneal factors influence ophthalmic drug bio availability:

- Volume of drop instilled
- Drug formulation
- Tear turnover
- Tissue absorption
- Tear protein binding

Radioactive suspensions instilled into human eyes show 2/3 reduction in radioactivity within 2 minutes and complete elimination within 15 minutes. It was also found that drainage of drug through nasolacrimal duct is more rapid than absorption across cornea.

The structural constraints and diffusional resistances that regulate the movement of the drug across ocular surfaces & within ocular tissues are summarized below. [Adapted from Maurice & Mishma (1984)]



a= aqueous, c= cornea, i=iris, p=plasma, pc=post chamber, t= tear reservoir, v= vitreous.

The cornea represents the major route for drug entry into the anterior chamber. Anatomically, the cornea consists of 5 layers: - epithelium, bowman's membrane, stroma, Descemet's membrane, and endothelium. In context of drug penetration, only the epithelium, stroma & endothelium are the significant permeability barriers. The epithelium is primary penetrant barrier. The basal cells in epithelium are packed closely together with a tight junction. Drugs penetrate across the corneal epithelium via the transcellular or paracellular pathway. Lipophilic drugs prefer the transcellular route.[3] And hydrophilic drugs penetrate primarily through the paracellular pathway which involves passive or altered diffusion through intercellular spaces.

Strategies in ayurveda

After understanding the major barriers in ocular drug absorption, let us understand the possible solutions. Ayurveda has applied following strategies to enhance drug absorption in ocular tissues.

(A) Precorneal drug retention and ayurveda

(a) Ayurveda has devised a technique to improve pre-corneal drug retention time by using pulsatile approach. It is achieved by instilling a large amount of drug in the form of aqueous drops, water solutions or milk solution over the period. Thus, in *Aschyotana* (eye drops),[4] a procedure where the medicines are used in the dosage of 7-12 drops over the period of 1½ - 4½ minutes at the rate of 4-26 drops/min is the intelligent modification of physiological barrier.

Table 2:

Type of *aschyotana*	Number of drops	*Matra* (time for holding /administration)	Frequency (a drop every -- sec)
Snehana (oleation)	10	200	8
Lekhana (scraping)	8	100	5
Ropana (wound healer)	12	300	10

(b)Furthermore, the drug used in a procedure called *Tarpana*, wherein the medicines are retained on ocular surface, for 05 to 10 minutes, with the help of temporarily formed retaining wall of gram flour along the orbital margin surrounding the eyeball,[5]

(B) Lipophilicity, hydrophilicity and ayurveda

Drug lipophilicity is one of the most important factors to determine its corneal penetrability. However, the hydrophilies nature of the stroma means that it can be rate limiting for highly lipophilic drugs, which become

retarred at the stromal -epithelial interface. Formulations, which possess an optimal balance of hydrophily & lipophilic properties, can therefore more rapidly permeate cornea.

The preparation used for *Tarpanam* And *Putapaka*[6] are classical examples of this in which the herbs are boiled with water and animal fat to extract their water soluble & fat-soluble contents and used topically to achieve higher trans corneal concentration. Although the cornea is considered the primary route for the drug entry into the eye, the roles of sclera & conjunctiva cannot be ignored.

(C) Conjunctival answer to corneal fuss

The conjunctival structure resembles a palisade and not a pavement when compared to the corneal epithelium. The conjunctival tissue is permeable to molecules up to 20,000 Da, whereas the cornea is impermeable to molecules larger than 5000 Da. making conjunctiva between 2 and 30 times more permeable to drugs than the cornea and it has been proposed that it is a major path for drug clearance. Conjunctiva is also permeable to the hydrophilic and large molecules.[7] Drugs absorbed by the noncorneal route appeared to enter certain intraocular tissues by a mechanism which bypasses the anterior chamber. These studies suggested that intraocular penetration via noncorneal routes involves penetration of drug across the conjunctiva/sclera. The palpebral &bulbar conjunctiva has equal permeability. The scleral permeability is half of the conjunctival permeability and ten times that of the corneal. It is poorly vascularized and consists mainly of collagen and mucopolysaccharides, through which drugs can diffuse and enter the posterior segment.[8]

Following corneal penetration, drugs are distributed into &then eliminated from the aqueous turnover and absorption into the tissues of the anterior area.

(C) Viscosity and Ayurveda

Increasing the viscosity with a carrier increases drug residence time and, in theory, the drug bioavailability (Bourlais, 1995). The drugs prepared in *Tarpana*, *Putapaka* and some *Anjana* have fat as a base [(6).] The contact of the drug to the ocular tissues is substantially increased with these formulations though the fat itself also interferes with tear film clarity, leading patients to complain of blurry vision or eyelashes being stuck together. Fats still have an important therapeutic role in the setting of corneal exposure or thermal burns, where production of tear film constituents has been disrupted or where the ocular surface is damaged (Fish and Davidson, 2010). Nevertheless, A non-aqueous, comfortable vehicle is desired for topical ophthalmic drug delivery because of drug degradation triggered by water or the premature leakage of the drug from the delivery system in the presence of water.

(D) Shear stress and Ayurveda

Shear stress is defined as the friction between two adjacent tissues, both of same or different physical states, when one or both are moved parallelly in relation to other. The procedures of *Tarpana*, *putapaka and anjan*a need either lid or eyeball movement periodically during the drug contact time which could be from 5 to 10 minutes or more. As shear rate increases, the gel "network" structure of the fat-water combination breaks down, and the viscosity of the system decreases. When the shear force is removed, the initial conditions restore, and the structure rebuilds rapidly. If structure recovers too quickly, the formulation will remain on the epithelial peaks. If recovery is too slow (or if there is no structure, as in Newtonian fluids), the formulation will flow into the epithelium's valleys. The sheer stress thus produced prolongs 'dynamic tissue-drug interaction time'. In this way, the epithelial absorption is enhanced with the help of applying sheer stress.

(E) Systemic absorption and ayurveda- All the topical administrations enter the nasal cavity & is absorbed readily across nasal mucosa, thus making it available for intracranial circulation also. Ayurveda is a holistic science. It considers the initiation of all eye diseases (except due to injuries) from the systemic imbalance amongst biological factors called *doshas* and thus, systemic actions of drugs are beneficial to correct the overall imbalance in those biological factors.[9] Furthermore, the medicines used are considered safe for systemic absorption producing enhanced effect.

CONCLUSION

In this article, the way in which the ocular tissues handle drugs and how drugs act have been discussed. In particular, the factor influencing the absorption, distribution, metabolism and excretion of ophthalmic drugs have been explained. This information will provide a foundation for an understanding of the further action of therapeutic agents used in ancient ophthalmology. Ayurvedic ocular topical preparations and methods depict clever application of law of physics and chemistry, pertaining to solubility, viscosity, and sheer stress. It also demonstrates the forgotten pathway of trans-conjunctival and trans scleral diffusion of drugs minimising the over emphasis on the corneal pathways. Since Ayurveda has a holistic rather than systemic approach towards pathology and therapeutics; the intracranial and systemic absorptions of the drugs are rather beneficial. The modern pharmaceutics should take a leaf from these ancient methods and develop newer methods of sustained and highly concentrated drug delivery system.

REFERENCES

1. Vaidyaraaj J. T. Acharya (editor). (6th edition). Nibandhasangraha commentary by Dalhana on Sushrutasamhita of *Sushruta* supplemented by

Nagarjuna, sharirasthana: chapter 18, verse no. 4, Varanasi: Choukhamba Orientalia, 1997; 633.
2. Ratain MJ, Plunkett WK Jr. Principles of Pharmacokinetics. In: Kufe DW, Pollock RE, Weichselbaum RR, et al., editors. Holland-Frei Cancer Medicine. 6th edition. Hamilton (ON): BC Decker; Available from: https://www.ncbi.nlm.nih.gov/books/NBK12815/, 2003.
3. Huang AJ, Tseng SC, Kenyon KR. Paracellular permeability of corneal and conjunctival epithelia. Invest Ophthalmol Vis Sci., 1989; 30: 684-689.
4. Vaidyaraaj J. T. Acharya (editor). (6th edition). Nibandhasangraha commentary by Dalhana on Sushrutasamhita of *Sushruta* supplemented by Nagarjuna, sharirasthana: chapter 18, verse no. 45, Varanasi: Choukhamba Orientalia, 1997; 636.
5. Vaidyaraaj J. T. Acharya (editor). (6th edition). Nibandhasangraha commentary by Dalhana on Sushrutasamhita of *Sushruta* supplemented by Nagarjuna, sharirasthana: chapter 18, verse no. 6-7, Varanasi: Choukhamba Orientalia, 1997; 633.
6. Vaidyaraaj J. T. Acharya (editor). (6th edition). Nibandhasangraha commentary by Dalhana on Sushrutasamhita of *Sushruta* supplemented by Nagarjuna, sharirasthana: chapter 18, verse no. 23-26 Varanasi: Choukhamba Orientalia, 1997; 634.
7. D.H. Geroski, H.F. Edelhauser, Transscleral drug delivery for posterior segment disease, Adv. Drug Deliv. Rev., 2001; 52.
8. I Ahmed, T F Patton; Importance of the noncorneal absorption route in topical ophthalmic drug delivery. *Invest. Ophthalmol. Vis. Sci.*, 1985; 26(4): 584-587.
9. Vaidyaraaj J. T. Acharya (editor). (6th edition). Nibandhasangraha commentary by Dalhana on Sushrutasamhita of *Sushruta* supplemented by Nagarjuna, sutrasthana: chapter 24, verse no. 8 Varanasi: Choukhamba Orientalia, 1997; 115.