Ophthalmic drug inserts

As far back as the turn of this century, ophthalmologists displayed lively interest in the problem of precise dosage of preparations instilled into the conjunctival sac and prolongation of their therapeutic effect. But despite the topical interest of this objective, medicinal agents used in ophthalmic practice have traditionally been applied in the form of eye drops or ointments. Yet accurate dosing of preparations used in this form is not possible. When eye drops are instilled into the conjunctival sac the drug is fairly rapidly evacuated with the tear whose secretion immediately becomes more intensive after instillation. Therefore, to attain a therapeutic effect, the number of instillations has to be increased 5- to 8-fold, or even more than that. If the solution is instilled into the conjunctival sac in a large amount it cannot immediately be taken up or absorbed by eye tissues and its excess partly flows out through the lower eyelid and partly penetrates the lacrimal canal causing irritation of the mucosa of the latter. Moreover, as a consequence of frequent instillations allergy to the drug may develop.

Development of more sophisticated pharmaceutical agents for ophthalmic practice is a promising way to attain precision in dosage of preparations and to prolong their effect. Along with ensuring more rational procedures for application of chemotherapeutic agents, solution of the problem of prolonging the therapeutic effect will contribute to the establishment and maintenance of optimal therapeutic concentrations of preparations in eye tissues over a long period.

To tackle the problem of prolongation, a synthetic vehicle such as polyvinyl alcohol (PVA) is the most popular viscosity-increasing agent used in ophthalmic preparations. The PVA solution gives a longer retention time and prolonged effect of medicinal preparations. The prolongation effect of preparations was further increased by polyacrylamide (PAA).

It was found that the retention time, prolongation effect of ophthalmic medications, and penetration of active material into the eye markedly increased with the PVA ophthalmic film (insert) device. The PVA ophthalmic inserts were easily slipped into or removed from the patient's lower conjunctival sac. After three hours' contact with the tetracycline PVA ophthalmic insert the concentration of the antibiotic in the conjunctival sac was: at three hours, 243.0 ± 5.7 μg per milliliter; at six hours, 39.6 ± 2.3; at nine hours, 7.7 ± 1.0; and at 24 hours, 3.4 ± 0.1 μg per milliliter. For comparison, after application of 1 per cent tetracycline oily solution, the concentration ratio of the antibiotic in the conjunctival sac was: at three hours, 3.7 ± 0.1 μg per milliliter; at six hours, 1.9 ± 0.04; at nine hours, 1.5 ± 0.1; and at 24 hours, 0.3 ± 0.1 μg per milliliter. PVA ophthalmic inserts were impregnated with antibiotics, sulfonamides, pilocarpine, atropine, and other drugs used in ophthalmology. The use of PVA inserts provides continuous control release, higher grade levels, and better penetration into the eye as compared with the application of ointments, suspensions, aqueous solutions, and viscosity-increased PVA solutions. Clinical observations have demonstrated the marked therapeutic efficacy of PVA ophthalmic inserts; yet it was observed that they, like polypeptides-polysaccharides ocular in-
Fig. 1.

Soluble ophthalmic drug inserts (SODI) have been suggested and developed by Y. Maichuk and G. Khromov in the Moscow Helmholtz Ophthalmological Institute in collaboration with the All-Union Research Institute for Medical Equipment, U. S. S. R. Following the results of an experimental study and clinical trial, SODI were endorsed for use in ophthalmic practice in the U. S. S. R. by a June 11, 1971 decision of the Pharmacological Committee, Ministry of Health.

SODI are made from polymers of polyacrylamide, ethylacrylate, and vinyl-pyrrolidone (molecular weights 200,000 to 750,000). SODI are prepared as thin elastic oval plates approximately 9 mm. by 4.5 mm. by 0.2 to 0.3 mm. An experimental and clinical study has been completed with SODI impregnated with neomycin, kanamycin, sulfapyridazine, idoxuridine, florenal (hydrogen sulphite, 2 glyoxal-fluoronunyl), atropine, pilocarpine, dexamethasone, dicaine (B-dimethylamino-ethyl-para-butyraminobenzoate), and some of their combinations. The method of obtaining SODI affords the possibility of avoiding significant variations of their weight, and drug dosages are thus more precise, this being a substantial advantage of this medicinal form. Routine pharmacologic methods were used to estimate changes of weight of SODI as well as changes of the shape, color, water absorption, mechanical robustness, dissolution rate, and the amount of preparation. The drug content in SODI is invariable, being 2.6 mg. for pilocarpine, 1.5 mg. for atropine, 1.0 mg. for neomycin, 5.2 mg. for sodium sulfapyridazine, 0.75 mg. for dicaine, and 1.0 mg. for idoxuridine. SODI can be sterilized and they do not change as a result of long-term storage (observation time: 12 to 18 months).

SODI are made of different colors in order to enable identification of the preparation they contain.

An experimental study on rabbits demonstrated that SODI were well tolerated by the eye tissue. No irritant or toxic effects were noted either during the treatment course or at a more remote time of observation; neither were any histopathologic changes detected. When inserted in the conjunctival sac of patients, SODI became rapidly wet with conjunctival liquid and dissolved in 30 to 90 minutes' time. The homogeneous solution formed in such a manner and carrying the drug facilitates a gradual penetration of the preparation into eye tissues. During the first minutes after insertion of SODI some patients have the sensation of the presence of a foreign body behind the eyelids.

In a comparative study, SODI offered a number of advantages over eyedrops (aqueous solutions, viscous solutions of polymers, and suspensions), ointments, and subconjunctival injections. In fact, their use makes it possible to obtain a prolonged bio-availability of active substances in the conjunctival fluid and conjunctival and corneal tissue.* In the case of sulfapyridazine, concentration of the drug in the eye tissue (conjunctiva/cornea) 24 hours after a single application of SODI was found to be 2.05/0.65 mg. per cent. At 48 hours the drug was still present at a fairly high concentration—1.1/0.23 mg. per cent. When 10 per cent sulfapyridazine in PVA solution was used, the respective concentration at 24 hours was 0.55/0.36 mg. per...
cent, but no drug was detected when an aqueous solution was used instead. Concentration of neomycin in the conjunctiva/cornea 24 hours after a single application was found to be 1.15/0.18 mg per cent for SODI, 0.20/0 for the 1 per cent neomycin PVA solution and 0/0 for aqueous solutions. Following a single application of SODI with kanamycin, the drug was detected in the conjunctiva in a concentration of 0.75 to 1.03 mg per cent after 24 hours and 0.56 to 0.6 mg per cent after 48 hours. When 1 per cent kanamycin aqueous solution was used no antibiotic was detected in the conjunctiva at 24 hours. Following a single application of SODI with pilocarpine, atropine, and idoxuridine, the drugs were detected in the conjunctiva at 24 hours and even at 48 hours at a fairly high concentration.

A nickelous chloride test showed that with SODI the retention time in the eye was increased to twice that of the PVA solution, to about 60 to 90 minutes. This long duration of pharmacologically or chemotherapeutically active concentration in the tissue surface secures the therapeutic concentration of preparations in the conjunctival sac, enhances the penetration of drug into the tissue and, therefore, may replace subconjunctival injections in certain cases. Following a single application of SODI with neomycin, the antibiotic was detected in rabbits' aqueous humor at one hour in 0.9 µg per milliliter and at three hours in 0.4 µg per milliliter concentration.

Experience gained during a clinical trial which covered more than 500 patients demonstrated a good tolerance and marked therapeutic efficacy of SODI in the treatment of different forms of glaucoma, corneal ulceration, herpes virus keratitis, iridocyclitis, conjunctivitis, trachoma, and paratrachoma. SODI, with the corresponding drug, are applied once daily or every other day for a maximum of 10 days, according to the nature of the disease and the condition of the patient. In subjects with severe forms of a disease, twice daily applications are required during the first two to three days. Two to three courses of repeated treatment are necessary in cases of trachoma. One single application of SODI with an antibacterial drug is effective for the prevention of infection after removal of foreign bodies from the cornea and also after ophthalmic surgery.

Precise concentration of drugs in SODI makes it possible to control dosage of preparations which is impracticable when eye drops and ointments are used; this is particularly important when medication is effected with a highly active substance. A simplified medication regimen of treatment with SODI is beneficial for the eyes and reduces the consumption of drugs used. This minimizes the danger of side effects produced by a number of preparations, such as allergic phenomena in the case of sulfapyridazine and antibiotics, disturbances under the action of atropine, and others. Since SODI are dissoluble in the conjunctival sac, there is no need to remove them. Owing to their prolonged action of up to 48 hours, the use of SODI makes it possible to save the time of the patient as well as that of the personnel involved.

Additional wide experimental and clinical studies are required for a full assessment and further development of ophthalmic drug inserts as a new medicinal form in ophthalmic practice.

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REFERENCES
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