DEVELOPMENT OF THE PHARMACEUTICAL COMPOSITION AND TECHNOLOGY OF COMBINED EYE DROPS FOR GLAUCOMA TREATMENT

A.N. Yakubchuk, E.G. Fetisova, L.N. Andryukova, S.N. Kovalenko
National University of Pharmacy, Kharkiv
e-mail: Larnik@mail.ru

Glaucoma is a disease that ranks top in the list of eye diseases and is an important medical and social problem, as evidenced by statistics on the number of patients with glaucoma and visually impaired people among them, chronic nature of untreated disease and irreversible loss of vision, difficulty of early diagnosis and the level of financial expenses for medical treatment. Pharmacotherapy of glaucoma is aimed at normalization of intraocular pressure (IOP), intraocular blood circulation improvement and normalization of metabolic processes in the retina and optic nerve, and includes multimodality therapy with several drugs having differently directed action. Improvement and development of new effective combined ophthalmic drugs with differently directed action, which would ensure not only normalization of IOP, but also minimal side effects and affordable to the general population, is always relevant. An earlier our study allowed substantiating relevancy and promising directions in combining drugs that affect different chains of pathogenesis, and creation based thereon of an effective drug in the form of eye drops. The aim of this study was the choice of the optimal pharmaceutical composition and the development technology of new combined eye drops for glaucoma treatment.

The objects chosen for investigation: an adrenergic receptor blocking drug and an amino acid derivative. To assess the quality of model mixtures the following methods were used: determination of clarity and degree of opalescence of liquids (SPU, 2.2.1) and degree of coloration of liquids (SPU, 2.2.2, Method II), potentiometric determination of pH (SPU, 2.2.3), capillary viscometer method (SPU, 2.2.9), determination of refractive index (SPU, 2.2.6), determination of osmolarity (SPU, 2.2.35), determination of conductivity (k) (SPU, 2.2.38), liquid chromatography (SPU, 2.2.29), absorption spectrophotometry ultraviolet (SPU, 2.2.25).

At the stage of pharmaceutical development combined hypotensive eye drops the behavior of drugs in aqueous solution depending on their chemical nature and pH of solution have been analyzed. Based on the calculated molar particle ions the optimum area of pH where drugs are present in the form of ions has been proved. The results of appearance of freshly prepared aqueous solution of drugs showed that at acceptable to eye drops pH range from 3,5 to 8,5 test solution is clear. This has

allowed to substantiate optimal range pH at which saved the stability of drugs in the form of aqueous solutions. A preliminary assessment of the compatibility of drugs in their joint presence in aqueous solution depending on the pH of the medium in terms of clarity, color, pH and electrical conductivity have been carried out. In the pH range of 3,5 to 8,5 aqueous solution of drugs in their joint presence has been clear and colorless, that indicate the presence of both drugs in the form of water-soluble ions. The value of conductivity of the solution of drugs in their joint presence, which is the sum of the values of electric conductivity of individual solutions of everyone drug, indicate no interaction between the studied drugs. The research allowed to prove scientifically the pH, which provides stability and comfort during application of eye drops that combined with drug substances of different chemical nature.

The chemical compatibility of drugs with the excipients from different chemical nature and with different functions, for example, such as buffer systems (phosphate, citrate, borate), tonicity agents (sodium chloride, propylene glycol, glycerin, mannitol), antimicrobial preservatives (benzalkonium chloride, methyl parahydroxybenzoate, propyl parahydroxybenzoate, decametoxin) viscosity and penetration enhancers (methylcellulose, hypromellose, povinilpirolidon, various species of dextrans, alginates, carbopols, polyethylene glycols) as well as various combinations thereof was studied.

According to the optimal values of physicochemical indexes of dosage form (osmolarity – 300-500 мOsm/l, pH – 6.0-7.5, refractive index – 1.333-1.357, viscosity- 1-30 mPa·s) the optimal pharmaceutical compositions of eye drops, which comply with modern requirements to ophthalmic medicines, were chosen.

The technological parameters of eye drops obtaining process of the pharmaceutical compositions in form of stable solution (order and temperature regime of ingredient dissolution, rate and duration of mixing) were studied. The compatibility of the different filter materials with the ingredients of eye drops was carried out and the process of eye drops filtration with the use of chosen filter materials was worked out. The complex research concerning development of the technology was determined considering typical schemes of eye drops production that exist at the domestic pharmaceutical enterprises. The study of influence of different primary packaging materials and storage conditions on stability of the eye drops during storage continues.

The complex research have helped to choose the optimal eye drops compositions and to develop the technology, which allowed to obtain the eye drops with indexes in accordance with SPU requirements of quality to ophthalmic drugs and there are acceptable physiologically to eye.