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Aspects of Getting Soft Medical Form of Fexofenodine for Curing Skin Allergic Deseases

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Abstract: The study proves the feasibility of developing a soft medical form of fexofenadine selected composition and developed a rational method of producing fexofenadine gel allows to obtain a drug with high bioavailability and optimum processability. The analyses of physicochemical compatibility of the anti-allergic gel components has been conducted using the Differential Scanning Calorimetry (DSC). The rheological and biopharmaceutical research of soft dosage form of fexofenadine has been conducted.

Key words: Antiallergenic products, gels, antihistaminic agents, fexofenadine, composition, drug

INTRODUCTION

In 21st century the problem of allergic disorders became one of the major issues of the modern health care system. There seeds of allergization of the population are still not determined and are subject to multiple arguments and discussions. According to the most widespread theory, the allergy development is caused by the decrease of antigen strength of people living in the civilized countries that are far from the nature. That's why the allergy belongs to the class of diseases caused by the civilization development.

Atopic dermatitis, antitoxin rash, neurodermatitis, eczema take a special place in the structure of allergodermathosises, the clinical implications of which have distinctive morphological traits of skin diseases (Baranova and Khaitova, 2010).

Soft forms of medical therapy are the most important parts of a complex treatment for the people suffering from allergic deceases that ensures the prompt penetration of a drug substance into the affected area (Korotkiy, 2001).

The major allergy mediator is histamine, a biologically active substance that takes part in the main metabolic processes, particularly in the immune decease resistance to an allergy. As histamine is directly in v olved into the mechanism of an allergy cardinal symptom's formation, antihistaminic drugs are administrated as a treatment of choice to cure skin allergies (Leonova, 2011).

Due to the leading role of histamine in the process of allergy reaction's evolvement and to the necessity of a complex treatment of allergic skin manifestations while having a limited assortment of soft medical forms for outward implication, the development of a new d e rmatologic form will allow to b roaden the nomenclature of antihistamine gels. Undoubtedly, this task becomes a relevant objective of the word pharmaceutical marketdevelopment.

The most prospective third generation antihistamine product is fexofenadine a powerful antihistamine drug with additional anti-inflammatory, antipruritic an anti-edematous effects.

It is also defined by a high pharma safety level if compared to the drugs of former generations (Vasilchuk *et al*., 2013; Weller *et al*., 2011; Simons and Simons, 2011; Wilson *et al*., 2002).

In the process of complex allergic and local effect's treatment one of the main advantages of exofenadine is its intense organotropy and much better skin penetration if compared with other antihistamine products (Kozachok *et al*., 2003). The fexofenadine substance is presented in the form of tablets and capsules. There is no soft form of fexofenadine (Handa *et al*., 2004; Dicpinigaitis and Gayle, 2003; Devillier *et al*., 2008).

There are a lot of different ointment bases presented on the world pharmaceutical market. The ointment bases are reported to provide a better drug bioavailability. From

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the point of the biopharmaceutics analyzing the biological effects of drugs according to their physical nature, form of administration and formulation, the maximum extrication of a drug substance takes place when infused into a saluted form of me dicament.

MATERIALS AND METHODS

The pharmaceutical substance of a third generation antihistaminic agent-fexofenadine hydrochloride (Regulatory Documentation 42 13016-04 with a content of fexofenadine 99.2%). In the evaluation process of the quality characteristics of a dosage form the following equipment was used: IR spectrometer with a Fourier transformer Vertex70 and a single attenuated total internal reflection adaptor Platinum ATR (Bruker, Germany).

Liquid chromatograph Milichrom 5 with a UV spectrophotometric detector and the wavelength range from 190 till 800 nm. A stainless still pipe 2.0×60 mm, Nucleosil C 18 was used as a stationary base. The pipe was full with an octadecylsilylendcapped silica gel of particles of 5 μ and 80 mm column l ength. As a mobile base a phosphate buffer was used: acetonitrile: methanol in the ratio 5:3:2. The stream velocity was 100 μ\min. The detection was effected at the wavelength 215 nm. The column temperature was 25±1°C. The analysis period was 20 min. The chromatographic run period was approximately 5 min. The range of a sample injection loop was from 5-100 μ with a tolerance to 0.2%.

Spectrophotometer Shimadzu UV-1800 (Japan), analytic wavelength of 228 nm, cuvette thickness 10 mm. A pH potentiometric determination was effected with pH-meter "150 M", OOO "ANTEH", Belorussia.

RESULTS AND DISCUSSION

During the process of a new fexofenadine dermatologic form research based on physical-chemical, biopharmaceutical and rheological studies the auxiliary substances were chosen as a good eluent of fexofenadine. These auxiliary substances enable the maximum bioavailability of fexofenadine and the most suitable structural-mechanical characteristics of a soft drug form Budtova.

The elaborated formula of fexofenadine gel consisted of a lightly crosslinked copolymer of an acroleic acid Carbopol (Technical Conditions 2219-005-290593342-97 RU), neutralized by a sodium hydrate solution (GOST RU 4328-77), glycerin was chosen as a preservative (Pharmacopoeial Item.2.20006.15 RU).

The technological scheme of 1% fexofenadine gel production is presented on Fig. 1. The specifics of the proposed method of fexofenadine gel production is that the actual substance is dissolved in the agent solution neutralizing Carbopol, densifying the system and making a gel structure with a fexofenadine at a molecular level. When adding fexofenadine alkaline solution to Carbopol solution, the polymer molecular arrangement takes a net structure which stabilizes and conserves fexofenadine molecules.

The pharmaceutical compatibility of the chosen formula was confirmed by a Differential Scanning Calorimetry method (DSC).

The research was done with the help of synchronous thermic analysis device, Model STA 449 F3 Jupiter, Software NETZSCH Proteus.

The heating curves of an examined soft dosage form can be seen on Fig. 2. These heating curves have no peaks of exothermic or endergonic reaction in the region of the temperature scenario of the technologic process which confirms the absence of chemical interaction among the components of a developing composition.

The comparative study of DSC-curves of fexofenadine gel and gel base presented on Fig. 3 clearly shows their identity which also testifies the absence of an interaction between the actual substance and the gel base.

An important indicator of medicine efficacy in a particular drug form is its bioavailability. By controlling the level of substance diffusivity though a permselective membrane *in vitro* experiments, it is possible to make a conclusion about the level of fexofenadine skin intake (Gladyshev, 2013). On Fig. 4, there is a release profile which was built on the base of experimental data of quantity definition of fexofenadine concentration converted to a dialysate.

As it appears from Fig. 4, the gel base of a Carbopol with a glycerin enables an equal, full and prolonged fexofenadine entry into the skin without reaching blood-vessels (penetrating effect of a gel).

The structural-mechanic features of a fexofenadine gel were analyzed with a traditional viscosity gage, type "Rheotest-II" (Germany). A fexofenadine gel is a thixotropic structure and it makes a hysteresis circuit loop, the width of which confirms the system structuredness. The gel is characterized by the high consumer properties, an optimized pasting and the stability when tube packing extrusion (Popova and Sakhanda, 2015).

By increasing the speed of cylinder rotation "Rheotest-II", the viscosity of the sample was decreasing, the structure was progressively deteriorating (Fig. 5). When the external input was withdrawn, the structure has

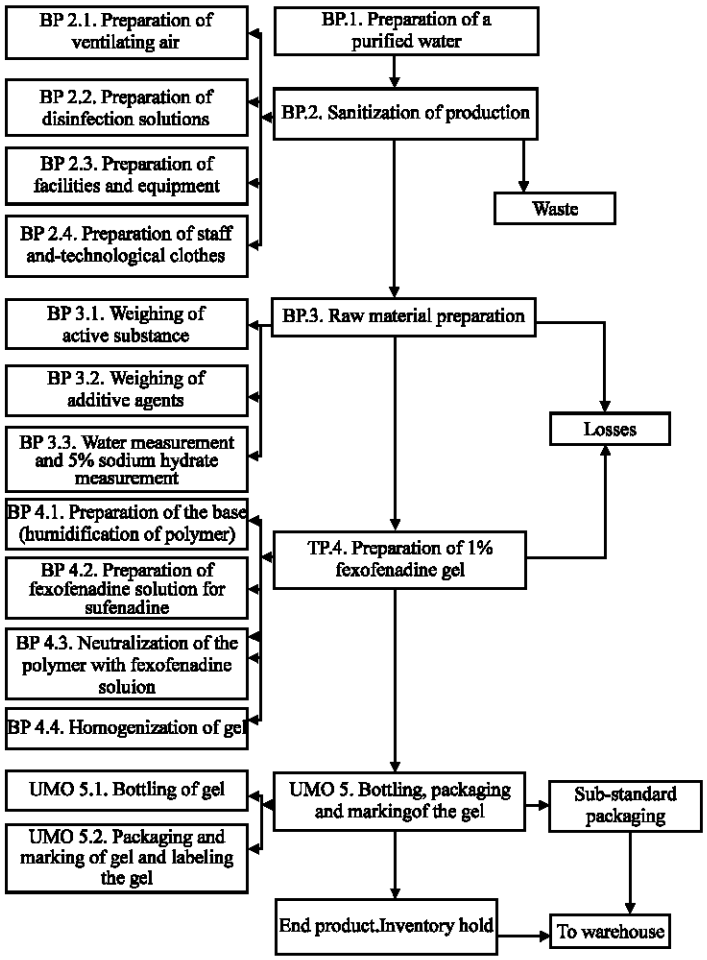

Fig. 1: The technological scheme of fexofenadine gel production

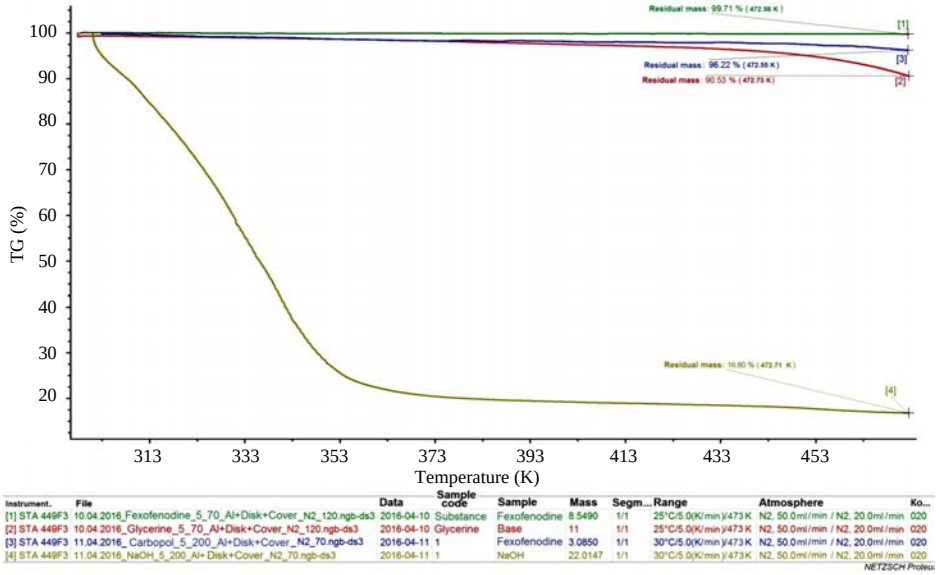

Fig. 2: DSC the curves of fexofenadine and auxiliary substances

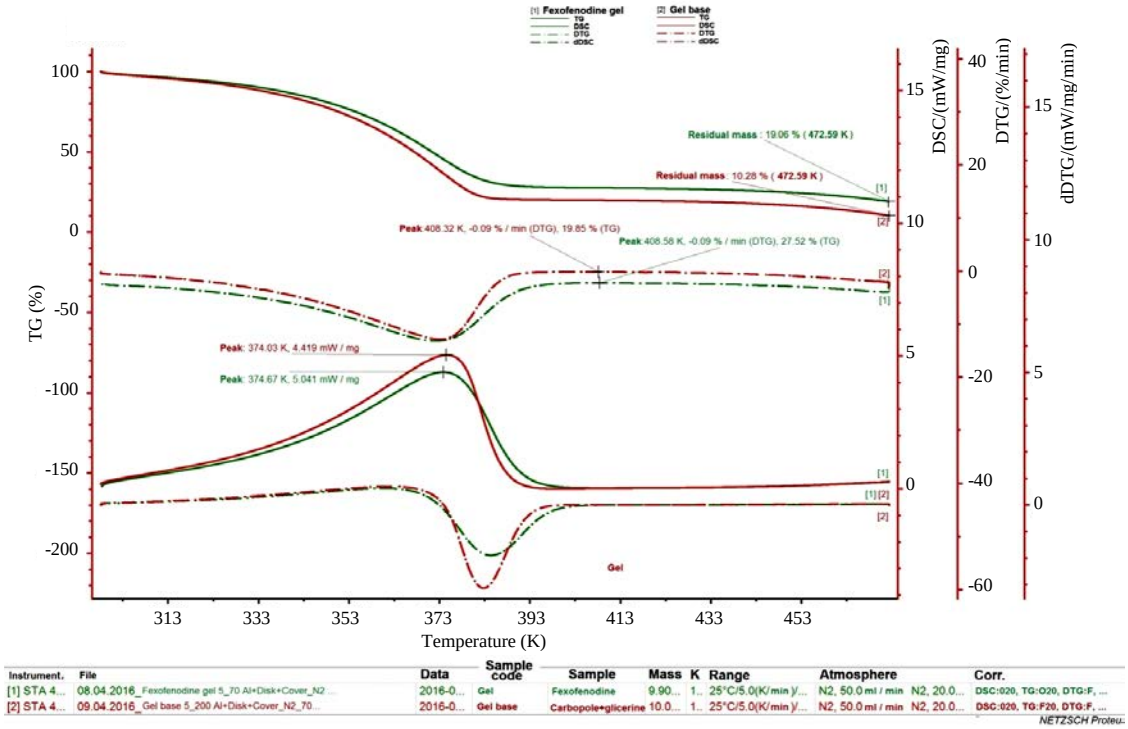

Fig. 3: DSC-curves of fexofenadine gel and gel base

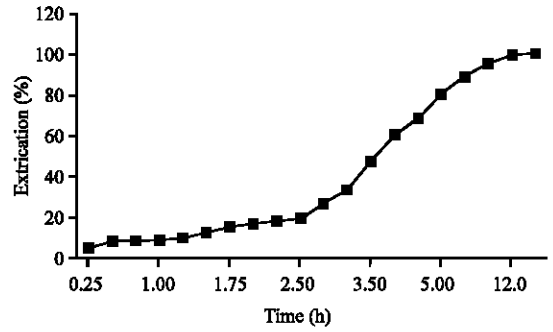

Fig. 4: Kinetic profile of fexofenadine's release from a gel

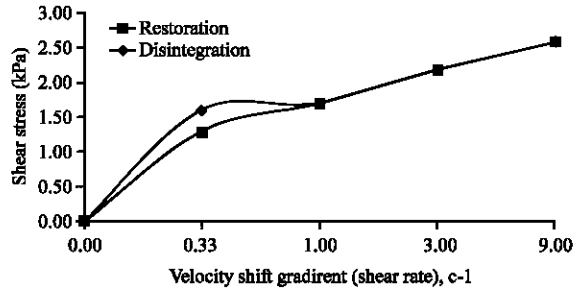

Fig. 5: The Rheogram of sample (#2)

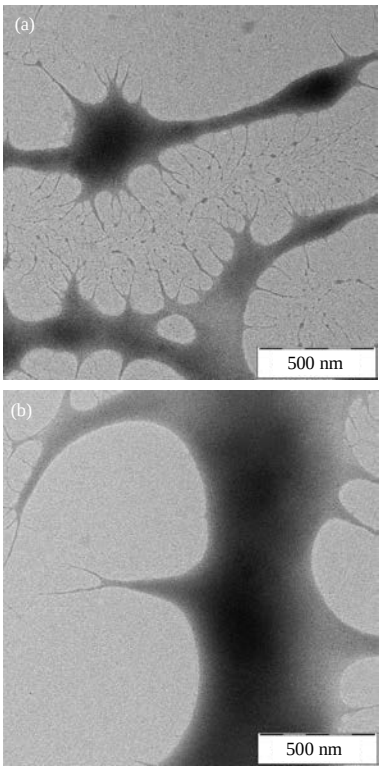

Fig. 6: A microscopic gel analysis: a) After being manufactured (left picture); b) After 30 months storage period (right picture)

restored by 85% which signified a benefit that enables the gel storage stability (Popova and Sakhanda, 2015) (Fig. 6).

Table 1: Specification "fexofenadine gel for outward application 1%"

Criteria	Determining methods	Standards
Description	Visual	A homogeneous transparent gelatin form mass of a white color and a slight characteristic smell
Authenticity	UV (Ultra-Violet)-Spectrophotometry (IR)	UV-spectrums of fexofenadine gel solutions and fexofenadine work standards in the range of 240-350 nm must have the maximum while being of the same wave-length. The analytical wave-lengthforms 228 nm
	Solution chromatography (Liquid chromatograph milichrom)	The retention time of the principal peak of the fexofenadine gel must correspond to the retention time of a standard fexofenadine sample. The retention time of fexofenadine counts in 5±0.5 min
	IR (infra-red)-spectophotometery (Spectrophotometer Shimadzu UV)	IR-spectrum must correspond to a standard sample of fexofenadine. The synchronism of bands can be observed at vibration of N-H link 3180-3350 cm^{-1} and C = O groups 1650-1670 cm^{-1}
The mass of package content	Gravimetric method (weighing)	According to the requirements
pH aqueousrecovery	Potentiometri cmethod A pH potentiometric determination	From 5.5 till 7.0
Microbialquality	Directinoculation method	Second category of quality, corresponding to external preparation
Quantitation	UV-spectrophotometry HPLC	Fexofenadine hydrochloride content must be 0.0095-0.0105 g in 1.0 g of the gel
Package	Dosage of 10, 15 and 30 g of the gel in a laminate tube. Each tube with an instruction for use is placed into a cardboard package	
Marking	According to the manufacturer's monograph	
Date of expiry	2 years	

In order to confirm the organoleptic parameters of fexofenadine gel a microscopic analysis was conducted, freshly prepared gel and gel after 30 months storage period. A microscope Libra 120 (ZEISSE) and a special technique of high energy electron diffraction zooming by 500 nm were used for this aim. The results of the analysis showed that the fexofenadine gel samples can keepits homogeneity and stability within 30 months (Fig. 6).

A fexofenadine gel keeps its homogeneity and physical-chemical stability during the whole storage period. Based on the undertaken technical studies, the special quality standards of the medical product "Fexofenadine, gel for outward application 1%" were worked out. These standards are presented in Table 1.

CONCLUSION

Therefore, based on the complex analysis results the advisability of a new antihistaminic dermatologic form was proved and a fexofenadine soft dosage form with optimal physical-chemical, biopharmaceutical, pheologicand pharmacologic characteristics was developed.

REFERENCES

Baranova, A.A. and R.M. Khaitova, 2010. Allergology and immunology under the general editorship. Union of Pediatricians of Russia, Russia.

Devillier, P., N. Roche and C. Faisy, 2008. Clinical pharmacokinetics and pharmacodynamics of desloratadine, fexofenadine and levocetirizine. Clin. Pharmacokinet., 47: 217-230.

Dicpinigaitis, P.V. and Y.E. Gayle, 2003. Effect of the second generation antihistamine, fexofenadine, on cough reflex sensitivity and pulmonary function. Br. J. Clin. Pharmacol., 56: 501-504.

Gladyshev, V.V., 2013. The analysis of the impact of carrier-bases on the intensity of the captopril release from nasal soft dosage forms. J. Kuban Sci. Med. Vestnik, 5: 69-73.

Handa, S., S. Dogra and B. Kumar, 2004. Comparative efficacy of cetirizine and fexofenadine in the treatment of chronic idiopathic urticaria. J. Dermatological Treat., 15: 55-57.

Korotkiy, N.G., 2001. Modern external therapy of dermatosis. Tver J. Gubernskaya Med., 5: 85-99.

Kozachok, N.N., L.V. Kuznetsova, A.P. Grishilo and I.N. Selyuk, 2003. Clinical efficiency of altive drug administration in the urticarial fever treatment. J. Dermatol., 4: 38-40.

Leonova, I.V., 2011. Modern antihistamines: The choice in the superfluity of proposals. J. Pharmateka, 10: 26-32.

Popova, Z.N. and I.V. Sakhanda, 2015. Rheologic characteristics and medical properties of soft dosage forms. Int. Sci. Inst. Educ., 9: 78-80.

Simons, F.E.R. and K.J. Simons, 2011. Histamine and H 1-antihistamines: Celebrating a century of progress. J. Allergy Clin. Immunol., 128: 1139-1150.

Vasilchuk, A.F., A.O. Ostapenko and A.I. Schekaturova, 2013. Treatment of allergodermathosis with a 3rd generation decongestant decongestant-altiva. J. Dermatology, 1: 40-41.

Weller, K., C. Ziege, P. Staubach, K. Brockow and F. Siebenhaar *et al*., 2011. H 1-Antihistamine up-dosing in chronic spontaneous urticaria: Patients' perspective of effectiveness and side effects a retrospective survey study. PloS. One, Vol. 6, 10.1371/journal.pone.0023931.

Wilson, A.M., L.C. Orr, W.J.R. Coutie, E.J. Sims and B.J. Lipworth, 2002. A comparison of once daily fexofenadine versus the combination of monte-lukast plus loratadine on domiciliary nasal peak flow and symptoms in seasonal allergic rhinitis. Clin. Exp. Allergy, 32: 126-132.