ТЕХНОЛОГІЯ ЛІКАРСЬКИХ ПРЕПАРАТІВ

Рекомендована д.ф.н., професором О.І.Тихоновим

UDC 615.454.811.014.015

PHYSICAL AND CHEMICAL SUBSTANTIATION OF THE METHOD FOR OBTAINING A MULTICOMPONENT LIPOSOMAL MEDICINE

G.I.Borschevsky, T.G.Yarnykh

«Pharmak» PJSC, Kiev, Ukraine
National University of Pharmacy

The work presents the physical and chemical substantiation of the method for obtaining a liposomal medicine in the form of a spray for treatment of wounds, which are non-healing for a long time, and necrotic skin lesions. Based on the study of the zeta potential of the drug disperse system the rational method – the method of high pressure with the number of dispersion cycles – 7 has been chosen. The stability of the medicine in the pH range of 4.0-6.5 has been proven. The isoelectric point is in the range of 2.9-3.05, the zeta potential is more than 30 mV.

Creation of medicines includes several stages of research, one of which is development of the optimal composition and technology. Physical and chemical indicators, namely zeta potential, are used for grounding of heterogeneous disperse systems stability.

It has been known for a long time [3, 8] that the zeta potential is a very good indicator of colloidal particles interaction value and it can be used for assessment of colloidal systems stability, for optimization of compositions of suspension and emulsion. Knowledge of the zeta potential can shorten the time required for drug research and forecast its stability [2, 10].

The mentioned above facts are of interest when developing a medicinal form on the basis of liposomes. In the given work to assess the choice of optimal technological parameters and the method for obtaining of a medicine the zeta potential has been chosen as an indicator fully characterizing the system in terms of stability.

The aim of the work is to ground experimentally the method for obtaining of a stable medicinal form on the basis of liposomes.

Materials and Methods

The medicine based on liposomes is a multicomponent system (5 components), and the main active substances are the concentrate of the deproteinized dermal layer of the pigs skin and phosphatidylcholine.

The medicine is being developed in the form of a spray under the conditional name «Efial» for treatment of non-healing wounds for a long time and necrotic skin lesions [1].

The technology for obtaining of the medicine based on liposomes includes the following technological stages: obtaining of the large liposomes emulsion (450-600 nm in diameter) and obtaining of the liposomes suspension (150-190 nm in diameter). The liposomes suspension of 150-190 nm in size was obtained by two methods: ultrasonic material dispersion and high pressure.

When obtaining the samples of the medicine the quantity of dispersion cycles was varied: 3, 5, 7.

The measurement of the zeta potential was carried out on a Zetasizer Nano device. The device uses a laser Doppler electrophoresis combined with M3-PALS. M3-PALS is the combination of the laser Doppler speed measurement and phase analysis light scattering.

Results and Discussion

If all of the particles in suspension have a large negative or positive zeta potential, then they will tend to repel each other, and it will prevent them from adhesion. However, if the particles have low values of the zeta potential, they will stick together and flocculate or settle. The common border between stable and unstable suspensions is generally taken as 30 or -30 mV. Particles with the positive zeta potential of more than +30 mV or with the negative one of more than -30 mV are generally considered to be stable. However, it is necessary to take into account the density of the dispersion medium [5, 6].

It is known that the zeta potential is influenced by pH, conductivity, and concentration of ingredients [7, 9]. The zeta potential compared to the pH curve is positive at low pH and it is low or negative at high pH. There may be the points where the graph crosses the zero zeta potential. It is called an isoelectric point and it is very important in practical consideration. Typically, these are the points where the colloidal systems are the least stable [11].

In this case, the zeta potential of a suspension of liposomes prepared by the method of high pressure with the number of dispersion cycles of 5 and 7 is shown in Fig. 1, 2. When the number of dispersion cycles is 3,

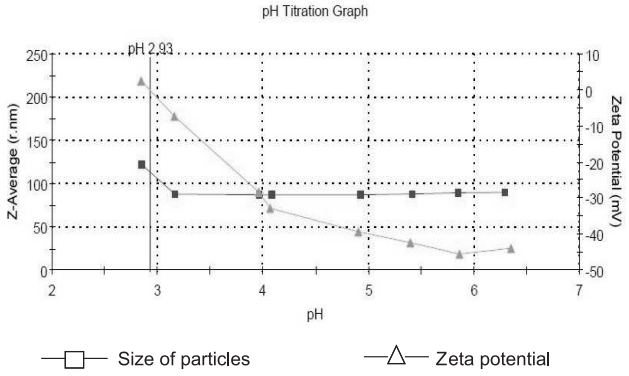

Fig. 1. The suspension of liposomes obtained by high pressure. The number of dispersion cycles – 7.

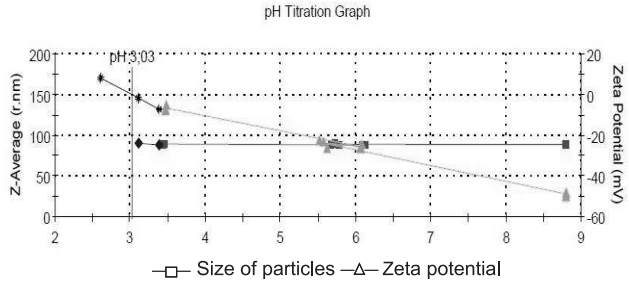

Fig. 2. The suspension of liposomes obtained by high pressure. The number of dispersion cycles – 5.

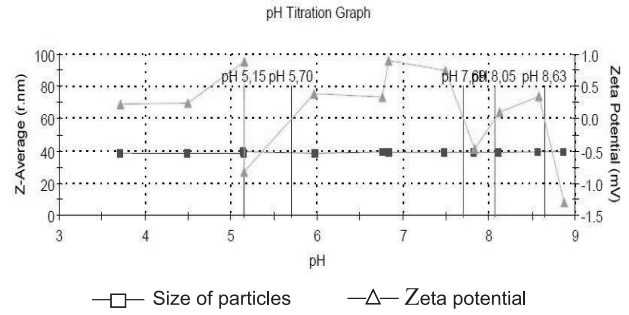

Fig. 3. The suspension of liposomes obtained by ultrasonic dispersion. Amplitude / power 90/60. Time 600 s.

the medicine was unstable, so measurement of the zeta potential was not carried out for this series. The research results have shown that stability of the system is achieved when the number of dispersion cycles is 7. The size of the particles throughout the pH range of 4.0-6.5 does not change, and the value of the zeta potential is more than 30 mV.

The isoelectric point of this sample of the medicine is beyond the pH range of 4.0-6.5. Its zeta potential is 0, i.e. the system is not stable, the particle size is more than 100 nm.

The results of these studies indicate that the medicine must be stable at pH more than 4.0 (a sufficient positive charge is present) and less than pH 6.5 (a sufficient negative charge is present). Problems with the stability of the disperse system developed can be expected at the pH less than 4.0 and more than 6.5.

Fig. 2 shows that when obtaining the medicine by the method of high pressure if the number of cycles is 5, the system is stable at a narrower range of pH values 5.5-6.5 mV.

Thus, if the number of dispersion cycles is 7, the system is more stable. It has been confirmed by the experimental study of stability of the medicine keeping its quality indicators throughout the pH range of 4.0-6.5 with the zeta potential of more than 30 mV. In the process of storage there is no decomposition of the drug dispersion system and, as a consequence, the content of basic and auxiliary substances in 1 ml remains unchanged.

The results of measuring the zeta potential of the liposomes suspension obtained by the method of ultrasonic material dispersion are shown in Fig. 3.

When obtaining the medicine by ultrasonic material dispersion the value amplitude / power: 90/60, 50/50 and 30/90 was varied at the given time 600 sec. In all cases the zeta potential is almost equal to 0 (Fig. 3). In this case, the medicine was not homogeneous and separated into layers. It indicates that the given method is ineffective for obtaining a liposomal medicine «Efial».

CONCLUSIONS

1. The rational method for obtaining the «Efial» medicine has been experimentally grounded; it is the method of high pressure. The stability of the medicine in the pH range of 4.0-6.5 has been proven. The isoelectric point is in the range of 2.9-3.05.

2. The optimal the number of dispersion cycles has been determined as 7, at which the value of a zeta potential is more than 30 mV, and it predicts its stability.

REFERENCES

1. *Пат. 101235 Україна МПК (2006) A 61 K 9/127, A 61 K 31/56, A 61 P 17/06. – Опубл.: 11.03.13. – Бюл. 5.*
2. *Dayan N., Touitou E. // Biomaterials. – 2000. – Vol. 21, №18. – P. 1879-1885.*
3. *Fairhurst D., Lee R. // Drug development & Delivery. – 2011. – Vol. 6, №6. – P. 60-64.*
4. *Fatouros D.G., Antimisiaris S.G. // J. of Colloid and Interface Sci. – 2002. – Vol. 251, №2. – P. 271-277.*
5. *Gallardoa V., Moralesa M.E., Ruiza M.A. et al. // Eur. J. of Pharmac Sci. – 2005. – Vol. 26, №2. – P. 170-175.*
6. *Gun'koa V.M., Zarkoa V.I., Lebodab R. et al. // Advances in Colloid and Interface Sci. – 2001. – Vol. 91, №1. – P. 1-112.*
7. *Miguel I.De, Imbertie L., Rieumajou V. et al. // Pharmac. Res. – 2000. – Vol. 17, №7. – P. 817-824.*
8. *Rathapon A., Sven-Iver L., Sunee S. et al. // Pharmac. Res. – 2007. – Vol. 24, №6. – P. 1098-1107.*
9. *Son K.K., Tkach D., Patel D.H. // Biochimica et Biophysica Acta. – Biomembranes. – 2000. – Vol. 1468, №1-2. – P. 11-14.*

10. Tabatt K., Kneuer C., Sameti M. et al. // J. of Controlled Release. – 2004. – Vol. 97, №2. – P. 321-332.

11. Wiącek A., Chibowski E. // Colloids and Surfaces A: Physicochemical and Engineering Aspects. – 1999. – Vol. 159, №2-3. – P. 253-261.

УДК 615.454.811.014.015

ФИЗИКО-ХИМИЧЕСКОЕ ОБОСНОВАНИЕ СПОСОБА ПОЛУЧЕНИЯ МНОГОКОМПОНЕНТНОГО ЛИПОСОМАЛЬНОГО ПРЕПАРАТА

Г.И.Борщевский, Т.Г.Ярных

В работе представлено физико-химическое обоснование способа получения липосомального препарата в форме спрея для лечения долго незаживающих ран и некротических повреждений кожи. На основании изучения дзета-потенциала дисперсной системы препарата выбран рациональный способ – метод высокого давления при количестве циклов диспергирования 7. Доказана стабильность препарата в диапазоне pH 4,0-6,5, изоэлектрическая точка находится в пределах 2,9-3,05, дзета-потенциал больше 30 МВ.

УДК 615.454.811.014.015

ФІЗИКО-ХІМІЧНЕ ОБГРУНТУВАННЯ СПОСОБУ ОТРИМАННЯ БАГАТОКОМПОНЕНТНОГО ЛІПОСОМАЛЬНОГО ПРЕПАРАТУ

Г.І.Борщевський, Т.Г.Ярних

У роботі представлено фізико-хімічне обгрунтування способу отримання ліпосомального препарату у формі спрею для лікування ран, що довго не загоюються, і некротичних пошкоджень шкіри. На підставі вивчення дзета-потенціалу дисперсної системи препарату обраний раціональний спосіб отримання – метод високого тиску при кількості циклів диспергування 7. Доведена стабільність препарату в діапазоні pH 4,0-6,5, ізоелектрична точка знаходиться в межах 2,9-3,05, дзета-потенціал більше 30 МВ.