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History of the Plaster-Based Drug Formulations' Development

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Abstract

The first drugs made in the form of a plaster appeared in ancient Egypt about 3 thousand years ago. Russian doctors have also been familiar with plasters for ages since dozens of different patches were made on the basis of fat, wax, resin, fine fabric and medicinal plants during the times of Ivan the Terrible. Then nobody suspected that in the second half of the 20th century an entire industry on manufacturing adhesive plasters for medicinal use would form where the plasters would differ on the composition of active substances, excipients, oils, and fat-like substances. The scope of the paper was to study the changes in the range of plaster-based drug formulations' types presented in the Russian Pharmacopoeia of 1802 to the present. Materials and methods included drug formulation, plasters, comparative analysis, content analysis. Plasters have been known since the ancient times. They were described in the writings of Galen and Hippocrates, and later - in those of Avicenna. Folk medicine also did not neglect it: all kinds of books of home cures and herbs certainly included recommendations for the manufacture of a wide variety of plasters. Comparative analysis of the State Pharmacopoeia - since the first edition of 1866 - clearly shows how the plasters have changed and improved with the development of science in general and medicine in particular. The State Pharmacopoeia also contained the first requirements for this drug formulation. In this article, we have followed the path of development and improvement of plasters over time: from the Ancient World to our days. The systematization and analysis of scientific and literary sources allowed determining that the plaster-based drug formulations had undergone significant evolution due to changes in their composition, modernization of external forms and production technologies, improvement of consumer properties, and improvement of quality.

Keywords: ancient world, bactericidal plaster, fixing plaster, history, medical form, pharmacopoeia, plaster.

INTRODUCTION

The plaster history has more than one thousand years, and for most of that time, it has evolved without any outbreaks and technological breakthroughs. Almost until the beginning of the 20th century plaster mass was prepared in pharmacies worldwide. For medicinal purposes, essential oils, balms, vegetable powders, crushed Spanish flies and even salts of heavy metals, often causing serious complications, were added to the base. We should count down the modern history of the plaster from 1882 onwards when the German pharmacist Paul Karl Byersdorf managed to invent a bactericidal plaster that did not cause skin irritations and prevented infection of wounds when healing. Throughout the history of civilization, plaster-based dosage forms have undergone significant evolution due to the progress of scientific knowledge. Some of them have disappeared, others – have improved over time. Practically the improvement of plasters occurred due to the expansion of the assortment of medicinal substances and excipients, intensification of technological processes of their production, and improvement of consumer properties. The products manufactured today can have very different bases: paper, fabric, plastic, silk. Plasters differ by the degree of air and moisture permeability, the presence of perforation, and size.

The present paper studies the changes in the range of plaster-based drug formulations' types presented in the Russian Pharmacopoeia of 1802 to the present.

MATERIALS AND METHODS

Materials: a medical plaster is a drug formulation containing one or several active substances, intended for external use and possessing the ability to adhere to the skin.

The methods used were the comparative and content analysis.

RESULTS AND DISCUSSION

The plaster drug formulation has been known to mankind since the ancient times: even the ancient Sumerian clay tablets mention the use of dressings containing honey and resin, which imparted this simple tool with the adhesive and disinfecting properties. In ancient Egypt, a strip of linen cloth impregnated with a mixture of oils and medicinal herbs was applied to the damaged skin. In ancient Greece, among other drug formulations for external use, the use of multicomponent plasters that could contain up to 20 components or more was common. The famous Greek physician Hippocrates noted that the plaster mass could not be applied to wound surfaces, so it was applied around the lesion and tied with a linen, well-absorbing detachable bandage [1].

In the ancient Rome, plasters were widely used not only for treatment but also for fixing bandages. For example, the ancient Roman doctor Aulus Cornelius Celsus believed that the main purpose of plasters was the application thereof to the undamaged skin to hold the bandage. The method of preparing such a drug was as follows: dry constituents in the form of powders were first mixed, and then - oil, wine or other solvent was added in drops. It is noteworthy that such an approach allowed plaster components to serve both as the agent and as excipients.

Diverse, ever-changing composition of plasters, where the active substances of mineral and animal or vegetable origin could be found, helped to systematize various forms of this drug formulation. Already then, in the second century of our era, arose one of the first classifications of plasters offered by the ancient Roman physician and philosopher Claudius Galen [2]. He divided the plasters into several types, taking the composition of the active substances as a basis:

1) Plasters containing metals (for example, plasters with lead oxide and copper rust used for drying wounds);
2) Plasters of juices and decoctions (for example, a plaster made of boiled dried figs, recommended for the treatment of septical wounds);
3) Plasters from crushed herbs (for example, a plaster made of honey mixed with cornflower and the roots of Illyrian iris for the treatment of fistula);
4) Plasters containing animal-based products in combination with other substances.

In the Middle Ages in the East, plasters were mentioned in the "Canon of Medicine" of Abū ʿAlī al-Ḥusayn ibn ʿAbd Allāh ibn al-Ḥasan ibn ʿAlī ibn Sīnā, known as Avicenna [3]. He described plasters of white lead, which were applied to ulcers and wounds, and analgesic plasters with vitriol used to dissect the abscess. For treatment of a liver tumour, Avicenna advised a plaster including such components as marcasite, sulfur and cumin. Waxes and resins, mixed with wine, were used as an agent with adhesive and softening properties.

Plasters were also widely used in ancient Russia, as well as in other countries of the time. At the time of Ivan the Terrible

(1547-1584), a large number of wax- and fat-based plasters were used as an agent using strips of fine fabric. This available remedy was used to treat both light wounds and bruises and ulcers, burns. The most popular mercury plasters appeared in Russia later, under Peter I [4].

The folk medicine made a huge contribution to the development of this drug formulation. The recipe of plaster from the book of home cures of 1791 is known: "Take four ounces of a crumb of white crumbled bread, two ounces of crushed mustard seed, an appropriate quantity of vinegar, and make a kind of plaster" [5]. It was recommended to apply the drug to the feet in case of fever. According to the same source, plasters based on dog's-tongue, hyoscyamus and tobacco were used as an analgesic and sedative agent.

The Russian Pharmacopoeia of 1798 translated into Russian in 1802 included the description of 10 types of plasters (Table 1), one of which - the mercury plaster - was used up to the 21st century [6]. In our opinion, the plasters presented in this Pharmacopeia can be classified into three groups:

- Lead plasters (litharge, sticky, glutinous compound, soap, mercury);
- Resin-wax plasters (wax, hemlock with ammoniac, sweet clover, abscess, or Spanish flies);
- Plasters with fish glue (English).

Table 1. The plasters presented in the Russian Pharmacopoeia of 1802, the Russian Pharmacopoeia of 1866 (1st edition) and the Russian Pharmacopoeia of 1891 (4th edition)

Plasters included in the Russian Pharmacopoeia of 1802	
Name	**Content**
English plaster (Emplastrum Anglicum)	Fish glue, benzoin gum, wine alcohol.
Hemlock plaster with ammoniac (Emplastrum cicutae cum ammoniaco)	Yellow wax, wood oil, hemlock extract, ammoniac, hemlock grass powder.
Wax plaster (Emplastrum citrinum)	Yellow resin, yellow wax, lamb fat, turpentine, powdered root of yellow ginger.
Litharge plaster (Emplastrum lythargyri)	wooden oil, litharge powder, vinegar.
Adhesive plaster (Emplastrum adhaesivum)	wooden oil, litharge powder, vinegar, adhesive plaster.
Sweet clover plaster (Emplastrum Meliloti)	White resin, lamb fat, yellow wax, wood oil, sweet clover grass powder.
Adhesive compound plaster (Emplastrum gummosum Diachylon compositum)	Litharge plaster, ammoniac, galban powder, turpentine.
Soap plaster (Emplastrum saponatum)	Litharge plaster, Vologda soap, camphor
Abscess or Spanish flies plaster (Emplastrum vegicatorium cantharidum)	Yellow wax, turpentine, powder of Spanish flies, camphor dissolved in wooden oil.
Mercury plaster (Emplastrum mercurial)	Litharge plaster; mercury, extinguished in turpentine
Plasters presented in the Russian Pharmacopoeia of 1866 (1st edition) [7]	
Adhesive plaster (Emplastrum adhaesivum)	Simple lead plaster, rosin.
White adhesive plaster (Emplastrum adhaesivum album)	Dammar tar, olive oil.
Green verditer plaster (Emplastrum Aeruginis)	White adhesive plaster, wax, turpentine, Green verditer powder.
Ammoniac plaster (Emplastrum ammoniac)	Wax, pine resin, a mixture of gum resins with turpentine, ammonia.
Ordinary blistering plaster (Emplastrum vesicatorium ordinarium)	Wax, rosin, bovine fat, turpentine and powder of Spanish flies.
Resinous Spanish flies plaster (Emplastrum vesicatorium perpetuum Janini)	Rosin, mastic, linseed oil, yellow wax, powder of Spanish flies.
bleaching plaster (Emplastrum Cerussae)	Lead oxide powder, wood oil, hot water, lead white powder.
Cicutae plaster (Emplastrum Cicutae)	Wax, rosin, wood oil, spotted omega powder.
Galbanum-saffron plaster (Emplastrum de Galbano crocatum)	Lead plaster, wax, a mixture of galbanum with turpentine, saffron powder, premixed with 90% alcohol.
Mynsichti diaphoretic plaster (Emplastrum diaphoreticum Mynsichti)	Wax, rosin, lead plaster, the mixture of turpentine with ammonia and galbanum, powder of myrrh, incense, mastic and amber.
Fetid plaster (Emplastrum foetidum)	Simple lead plaster, a mixture of turpentine with ammonia.
Mercury plaster (Emplastrum hydrargyri)	Mercury ointment, mercury, lead plaster, wax, turpentine.
Bleach plaster (Emplastrum Hyoscyami)	Wax, rosin, wood oil, henbane leaves powder.
Brown plaster (Emplastrum Matris)	Lead plaster, pork fat, cow oil, bovine fat, wax, black resin.
Sweet clover plaster (Emplastrum Meliloti)	Wax, rosin, bovine fat, sweet clover grass and a mixture of indigo and turmeric.
Black resin plaster (Emplastrum Picis nigrae)	Black tar, pine resin, turpentine, wax.
Complex lead, diachil plaster (Emplastrum Plumbi compositum)	Simple lead plaster, wax, a mixture of gum resins with turpentine.
Simple lead plaster (Emplastrum Plumbi simplex)	Wooden oil, water, lead oxide powder.
Soap plaster (Emplastrum saponatum)	Simple lead plaster, wax, Spanish soap powder.
Schiffhauseni plaster (Emplastrum Schiffhauseni)	Minium, white, wood oil, hot water, rosin, Spanish soap powder, camphor powder.
Tartaric emetic plaster (Emplastrum Stibio-Kali tartarici)	Resin plaster, tartaric emetic powder.
Plasters presented in the Russian Pharmacopoeia of 1891 (4th edition) [8]	
Adhesive plaster (Emplastrum adhaesivum)	Simple lead plaster, rosin, petrolate.
Ordinary Spanish fly plaster (Emplastrum Cantharidum ordinarium)	Wax, rosin, turpentine, powder of Spanish flies.
Resinous Spanish fly plaster (Emplastrum Cantharidum ordinarium)	Wax, rosin, fat, turpentine, powders of Spanish flies and euphorbia
Blister Plaster (Emplastrum Cerussae)	Lead oxide powder, wood oil, hot water, lead white powder.
Mercury plaster (Emplastrum hydrargyri)	Mercury, lanolin, pork fat, lead plaster.
Sweet clover plaster (Emplastrum Meliloti)	Wax, rosin, wood oil, sweet clover grass.
Complex lead plaster or gummy plaster (Emplastrum Plumbi compositum)	Gummy resin, turpentine, lead plaster, wax,
Simple lead plaster (Emplastrum Plumbi simplex)	Lead oxide powder, water, wood oil, pork fat.
Soap plaster (Emplastrum saponatum)	Lead plaster, white wax, soap powder, camphor, melted in olive oil.
English plaster (Sticky Taffeta)	Fish glue, water, alcohol, glycerin, tincture of benzoic resin.

Table 2. Plasters presented in the 4th edition of the Russian Pharmacopoeia, in the 7th and 8th editions of the State Pharmacopoeia of the USSR

Pharmacopoeia / Plaster name	Russian Pharmacopoeia, 4th edition (1891)	State Pharmacopoeia of the USSR, 7th edition (1937)	State Pharmacopoeia of the USSR, 8th edition (1952)
Blister Plaster (Emplastrum Cerussae)	+	-	-
Sweet clover plaster (Emplastrum Meliloti)	+	+	+
Sticking plaster (Emplastrum adhaesivum elasticum extensum)	-	-	+
Adhesive plaster (Emplastrum adhaesivum extensum)	+	+	-
Soap plaster (Emplastrum saponatum)	+	+	+
Mercury spread plastered (Emplastrum hydrargyri extensum)	-	-	+
Spanish fly plaster (Emplastrum Cantharidis)	+	+	-
Simple lead plaster (Emplastrum Plumbi simplex)	+	+	+
Mercury plaster (Emplastrum hydrargyri)	+	+	+
Complex lead plaster (Emplastrum Plumbi compositum)	+	+	+
English plaster (Sticky Taffeta)	+	-	-

In Europe in 1845, physician Horos Harrell had invented a plaster, which became the first step to a modern sticking plaster. It was a fabric strip with a rubber-based adhesive layer. Substances of the plaster caused severe skin irritation, so the skin was powdered with talcum powder to reduce the side effect. Almost at the same time in Paris, a liquid patch was invented - an easily volatile liquid leaving a strong elastic film on the skin after application (http://hroniki.org/articles/bint-istoriya-perevyazochnogo-materiala).

The general article "Plasters - Emplastra" appeared in the first edition of the Russian pharmacopoeia only in 1866. It contained the basic requirements for this drug formulation: homogeneity of the plaster mass and the absence of foreign substances therein, which was achieved by melting the components and straining the resulting mixture through the canvas. Plasters were packed in paper capsules. Plasters in the form of cylindrical sticks or spread over the cloth or kid leather were packed in waxed paper, which was placed between two plaster sticks or tablets to prevent their sticking [7]. The first edition of the Pharmacopoeia included private articles for 21 plasters (Table 1). This composition of plasters included resins, gums, turpentine, wax, fat, powders, extracts, soaps and other substances. Subsequently, such plasters became known as ordinary as opposed to rubber ones, which were first described in the 5th edition of the Russian Pharmacopoeia.

In 1882, the German pharmacist Paul Karl Byersdorf created a plaster by spreading a mixture containing rubber, resin and a disinfectant solution over a linen cloth. Later, zinc oxide was added to the plaster composition, which significantly reduced the irritating effect of the adhesive backing, and the plaster itself acquired a white color. This way the world's first bactericidal adhesive plaster appeared. However, this plaster was not included in the 4th edition of the Russian pharmacopoeia [8], published in 1891, and the number of official plasters significantly decreased in comparison with the previous Pharmacopoeias: the fourth edition contained only 10 private articles on plasters (Table 1). In 1876, Yu.K. Trapp stated: "Unfortunately, the number of official plasters is still considerable, although most of the doctors stopped using them, with the exception of plasters made from Spanish flies and sticky ones." This statement explains the reduction in the number of private articles on plasters in the 1st-4th edition of the Russian pharmacopoeias

In the United States of America, Johnson & Johnson employee Earl Dickson developed his own version of the plaster - a sticky tape on which dense gauze bandages were glued, and the invention itself rolled into a roll and was fixed with special stickers. Soon, a serial production of such products, called "band-aid", started. At first, they were not popular since the width of the adhesive tape of up to 10 centimeters created certain inconveniences in use. Soon this defect was corrected, and the plasters acquired a form close to modern fixing plasters in coils (http://professiya-vrach.ru/article/istoriya-izobreteniya-bakteritsidnogo-plastyrya/).

In Russia, mass-production of plasters was launched in 1944 by the Veropharm company. Initially, a band-aid was produced in a coil. In 1959, the production of adhesive plaster with greenery was launched, in 1960 - the production of a corn-plaster, and in 1961 - that of pepper plaster. Only in 1946, the plaster was officially included in the 8th edition of the State Pharmacopoeia of the USSR (Table 2). The same Pharmacopeia was the first which listed the definition of plasters as a medicinal form for external use, which had the ability to soften and adhere to the skin [9].

Of the plasters manufactured in the period from the end of the 18th century to the beginning of the 20th century, only simple lead plaster, adhesive lead plaster and collodion are currently produced.

Over time, the technology of making plasters has been improving. Water-soluble acrylate gels were used in the production of plasters, allowing to significantly reducing the irritating effect on the body and causing hypoallergenic properties. Hydrocolloid plasters, protecting skin and wound surface, allowed to partially replace bactericidal plasters.

Transdermal patches designed for controlled drug delivery into the bloodstream and having systemic effects on the organism have become one of the most promising developments [10].

Transdermal systems are a complex advanced drug formulation, working on the principle of plaster. The modified release of active substances in them occurs on the passive diffusion principle. They include a reservoir of medicinal substances and a material that acts as an outer barrier layer. Due to the membrane of the reservoir with the active substance and the contact adhesive coating of the transdermal system, a dose-controlled delivery of the drug substance takes place. The active substances that determine the pharmacological activity of the drug enter the systemic circulation, penetrating through the skin or mucous membrane due to the concentration gradient on both sides of the semipermeable membrane, which, in this case, is represented by the skin or mucous membrane. The feature of the transdermal system is maintaining the concentration of active substances at a certain level for a long time. This property is especially important in cases of chronic pain, various forms of dependence, chronic hypovitaminosis. Examples of such transdermal systems that appeared in the Russian Federation in 2010-2014 are Voltaren, Ketonal, Rotigotine, Fentanyl, Nicotine, Diclofenac, Norelgestromine + Ethinylestradiol and other transdermal systems. Such pharmaceutical companies as Novartis

Pharma AG (Switzerland), Sandoz d. (Slovenia), Gedeon Richter (Hungary), Johnson & Johnson (Sweden) succeeded in developing this drug formulation (https://grls.rosminzdrav.ru/Default.aspx).

Currently, the technologies of producing plasters continue to improve. Scientists from the University of North Carolina, USA are developing an insulin plaster that will allow people with diabetes to get rid of numerous injections of insulin. It will be a silicone strip covered with numerous tiny needles, with microscopic containers for insulin at the base. It is enough to attach such a plaster to the skin and with an increase in sugar in the blood, insulin is released and enters the subcutaneous area, and then - into the blood (http://www.vesti.ru/doc.html?id=2633274&cid=2161).

The US Center for Disease Control and the Georgia Institute of Technology have announced a project for a new micro-needle plaster that can replace syringes for vaccination. It will be a strip with micro-needles made of a mixture of polymer, sugar and vaccine. In order to get vaccinated, it is enough to attach the plaster to the skin. Microneedles penetrate the upper layers of the skin and dissolve, releasing the vaccine (https://medbe.ru/novinki/plastyr-s-mikroiglami-dlya-bezboleznennykh-privivok/). The advantages of such patches are the ease of use, safety, atraumaticity, and practicality.

The constantly updated wide range of patch applications allowed them to become a fixture in the pharmaceutical market. The growing demand for this dosage form only confirms the assertion that today there is hardly anyone who does not know about plasters.

CONCLUSIONS

The systematization and analysis of scientific and literary sources allowed determining that the plaster-based drug formulations had undergone significant evolution due to changes in their composition, modernization of external forms and production technologies, improvement of consumer properties, and an increase in quality.

REFERENCES

1. Abayev, Yu.K., Istoriya ranevoy povyazki [History of wound dressing], *Meditsinskiye novosti* 2003, *6*, 73-81.
2. Galen, *Sochineniya* [Compositions], Practical Medicine, Moscow 2015, p. 24.
3. Avicenna, *Canon of Medicine*, Vol. 1-5, Fan, Tashkent 1979-1982.
4. Seletskiy, A., Plastyri: Istoriya, sovremennost', perspektivy [Plasters: History, modernity, prospects], *Aptekar'* 2014, *4(1)*.
5. Buchanr, W., *Polnyy i vseobshchiy domashniy lechebnik: Tvoreniye g. Bukhana, slavneyshago v nyneshnem veke anglinskago vracha* [Complete and universal book of home medicine: The creation of Bukhan, the most famous in the present century Anglin physician], Vol. 4-5, V. Okorokov, Moscow 1790-1792.
6. Karpinskiy, N.K., *Farmakopeya Rossiyskaya*, Senate Printing House of Selivansky, Moscow 1802.
7. Trapp, Y.K., The Russian Pharmacopoeia, Vol. 1-2, 1866.
8. Trapp, Y.K., The Russian Pharmacopoeia, Vol. 1-2, 4th ed., 1891.
9. USSR Ministry of Health, State Pharmacopoeia of the Union of Soviet Socialist Republics, Medgiz, Moscow 1952.
10. Belousov, Yu.B., Bukhman, V.M., Erofeyeva, S.B., Leonova, M.V., Maneshina, O.A., Mukhina, M.A., Strok, A.B., *Lekarstvennyye formy s modifitsirovannym vysvobozhdeniyem i sistemy dostavki lekarstv: osobennosti farmakokinetiki i klinicheskaya effektivnost'* [Modified release dosage forms and drug delivery systems: features of pharmacokinetics and clinical efficacy.], Litterra, Moscow 2011.