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SERIAL PRODUCTION OF DOMESTIC BIOACTIVE GLUE FOR MEDICAL PURPOSES



New domestic biologically active medical glue has been developed for the application to implantation, dermatoplasty, bonding or fixation of soft tissues and bones, as well as for the stimulation of regeneration process. Comprehensive biomedical research, preclinical, clinical, and certification tests have been carried out. Technical documentation has been prepared and approved. Serial production of medical glue has been organized at the Medical Polymers Department of the Institute for Chemistry of High-Molecular Compounds of the NAS of Ukraine.

Keywords: glue, folic acid, biological activity, biocompatibility, medicine, and regeneration.

RELEVANCE AND RESULTS OF THE R&D PROJECT

The adhesive agents destined for grafting, gluing, and fixing tissues, bones, and pieces of skin are very important for surgical, reconstructive, and plastic operations. The use of synthetic glues with good adhesive properties enables abandoning the conventional fixation methods (stitching) and improving the techniques and quality of surgeries, which leads to reduction of time of surgery and decrease in frequency of complications by more than 30%. The medical glues help avoid deformation and compression of vascula and tissues in surgeries, raise strength of joints, reduce time of hemostasis and blood loss, and speed up medical and social rehabilitation of patients.

Within the framework of R&D project «Organization of Commercial Production of Ukrainian Bioactive Glue to be Used for Medical Purposes», a procedure for pilot production has been designed, and a pilot batch of medical glue for preclinical, clinical, and certification studies has been manufactured.

The medical glue is a three-component system consisting of the *adhesive base* (oligoester urethane diisocyanate), the *polymerization accelerator*, and the *bioactive filler* (folic acid). In the humid environment of the wound, the glue foams thereby forming a fine-porous elastic mass. Due to this, the polymer has an extensive surface and a large contact area with tissue; it is notable for by a high biocompatibility, not toxic, and does not have any allergic effects on the surrounding tissue. The prolonged local effect of folic acid introduced into the adhesive base helps accelerate the regenerative processes in the place of glue application. The medical glue forms an adhesive seam which firmly holds the tissues at all stages of the wound repair and the cicatrix formation.

Medical glue TU U 21.2-05417041-024:2013 has passed preclinical studies at the Medved National Center for Preventive Toxicology, Food and Chemical Safety of the Ministry for Healthcare of Ukraine. Upon the results it has been established that medical glue TU U 21.2-05417041-024:2013 is safe for the use in accordance with respective guidance and is recommended for registration as medical product. Upon the results of state sanita-

ry and epidemiologic examination the report on the medical glue TU U 21.2-05417041-024:2013 has been made. Pilot samples of medical glue TU U 21.2-05417041-024:2013 has passed clinical studies at the Shupik National Medical Academy of Postgraduate Education. Upon the results of clinical studies, it has been established that medical glue is safe for its intended purpose and complies with the advanced requirements of medical practice. To register this medical product at the State Service of Ukraine for Medical Products, the qualification tests have been made. Upon their results it has been established that medical glue TU U 21.2-05417041-024:2013 is suitable for use.

Upon result of preclinical, clinical, and qualification studies the medical glue TU U 21.2-05417041-024:2013 has been registered at the State Service of Ukraine for Medical Products of the ministry of Healthcare of Ukraine, with Certificate of State registration of medical product no.13329/2013 of 27.06.2014 issued; TU U 32.5-05417041-022:2013 was approved at the Ukrainian State R&P center for Standardization, Metrology, and Certification (Ukrmetteststandart), state-owned enterprise.

Hence, comprehensive medical and biological studies, as well as preclinical, clinical, and qualification tests, technical documents and registration/approval have enabled organizing serial production of medical glue at the Medical Polymers Department of the Institute for Chemistry of High-Molecular Compounds of the NAS of Ukraine.

USERS OF R&D PROJECT DELIVERABLES

Potential users of medical glue are hospitals, institutes, and educational establishments of the Ministry of Healthcare of Ukraine, which have specialized departments in polyclinics and carry out surgical, reconstructive, and plastic operations.

Ukrainian- and Foreign-Made Medical Glues

The existing counterparts of the abovementioned glue are tissue glues of biologic and synthetic origin, with fibrin-containing composites being the most widespread among the former [1, 2]. They are used



Medical glue

mainly in abdominal operations, but their application is limited for some reasons. *Firstly*, the stitches treated with fibrin glues do not bear large strain, *secondly*, they contain a biological material which is associated with risk of virus contagion; and finally, the production of fibrin glues is very expensive.

The most widespread synthetic glues are cyanoacrylate composites [2–5]. These glues are based on esters of cyanoacrylate acid. They are notable for high reactivity and fast polymerization in the air environment. Methyl-2-cyanoacrylate and ethyl-2-cyanoacrylate were the first cyanoacrylate to be used for clinical studies. These glues caused acute inflammation of tissues. One more glue, butyl-2-cyanoacrylate, is remarkable for satisfactory adhesive properties and is lesser toxic for the tissues. This glue has been authorized for application in Canada, Europe, and Japan where it has been being widely used in traumatology and surgery during recent 20 years (trademarks *Gluestitch*, *Liquiderm*, *Nexaband*). Among cyanoacrylate modifications, there is octyl-2-cyanoacrylate known under the trademark of *Dermabond* [6, 7], the most advanced cyanoacrylate glue that does not have many disadvantages typical for its predecessors, however, it is very expensive for wide application in Ukraine.

The disadvantages of cyanoacrylate adhesives are as follows:

- ✦ Hydrophobic properties and necessity of drying the surface (in some cases, with aggressive driers) before the application of glue;

- ✦ General and local toxicity;
- ✦ Exothermic effects during glue polymerization, which lead to local thermal imbalance and can cause burn of tissues, necrotic effects, enhanced peritoneal process, inflammatory and infiltratory changes in surrounding tissues;
- ✦ Presence of toxic flexible agents/plasticizers (for instance, dibutylphthalate);
- ✦ Extremely fast hardening of the film and, as a result, poor adhesion to tissues, which can lead to rejection of adhesive film at early postsurgical period, resumption of bleeding or disruption of wound;
- ✦ Insufficient elasticity of polymerized film impairing the functional activity of locomotive organs;
- ✦ Long biodegradation (over 1.5 years).

The above listed shortcomings of the adhesives for joining tissues put limitations on their use in surgery and entail searching new glues based on other polymers [8].

Among the counterparts, the latex glue for tissues manufactured by North-West (Russia, Saint Petersburg, a member of Association of Medical Industry Corporations, has the most similar composition and destination to the medical glue TU U 21.2-05417041-024:2013. It is used for sealing anastomoses, repairing wounds of abdominal organs, stopping parenchymal bleeding, and covering surfaces of parenchymal organs [9]. This glue is notable for high adhesion to living tissues, biocompatibility, it is hydrophilic and biodegradable, possesses bactericide and hemostatic properties. However, the latex glue for tissues neither stimulates regenerative processes nor can be used for sealing of tissue defects. In addition, its production is quite expensive.

Key Advantages of Medical Glue TU U 21.2-05417041-024:2013

The medical glue is a composite based on cross-linked polyurethane having a composition that principally differs from the existing foreign and domestic counterparts. It is notable for high adhesion to living tissues, hydrophilic and is polymer-

ized during 5 minutes in surgical wound creating an elastic fine-porous sponge that does neither misshape the surrounding tissues nor impair their functional activity. It forms a glued seam that firmly fixes the tissues at all stages of wound repair and cicatrix formation, stimulates regenerative processes. The glue is remarkable for absence of toxic and cancerogenic effects, high biocompatibility and biodegradability in the organism. One of the key advantages of this glue is its low cost as compared with the foreign counterparts.

Recommendations Related to Implementation of the Project Results

Medical glue TU U 21.2-05417041-024:2013 (see Figure) can be widely used in maxillofacial, decorative, reconstructive, orthopedic, and oncologic surgeries. Practical application of medical glue enables to abandon fully or partially its import thereby saving money, supporting the national producers and raising their competitiveness.

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**ОРГАНІЗАЦІЯ СЕРІЙНОГО
ВИРОБНИЦТВА ВІТЧИЗНЯНОГО
БІОЛОГІЧНО АКТИВНОГО КЛЕЮ
ДЛЯ ВИКОРИСТАННЯ В МЕДИЦИНІ**

Розроблено новий вітчизняний біологічно активний медичний клей, призначений для імплантації та пластики дефектів м'яких тканин та кісток, склеювання або фіксації м'яких тканин та кісток, а також для прискорення процесу регенерації. Проведено комплексні медико-біологічні дослідження, доклінічні, клінічні та кваліфікаційні випробування, розроблено технічну документацію, проведено її реєстрацію/узгодження. В процесі виконання науково-технічного проекту організовано серійне виробництво клею медичного на базі відділу полімерів медичного призначення Інституту хімії високомолекулярних сполук НАН України.

Ключові слова: клей, фолієва кислота, біологічна активність, біосумісність, медицина, регенерація.

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**ОРГАНІЗАЦІЯ СЕРІЙНОГО
ПРОИЗВОДСТВА ОТЕЧЕСТВЕННОГО
БИОЛОГИЧЕСКИ АКТИВНОГО КЛЕЯ
ДЛЯ ИСПОЛЬЗОВАНИЯ В МЕДИЦИНЕ**

Разработан новый отечественный биологически активный медицинский клей, предназначенный для имплантации и пластики дефектов мягких тканей и костей, склеивания или фиксации мягких тканей и костей, а также для ускорения процесса регенерации. Проведены комплексные медико-биологические исследования, доклинические, клинические и квалификационные испытания, разработана техническая документация, проведена ее регистрация/согласование. В ходе выполнения научно-технического проекта организовано серийное производство медицинского клея на базе отдела полимеров медицинского назначения Института химии высокомолекулярных соединений НАН Украины.

Ключевые слова: клей, фолиевая кислота, биологическая активность, биосовместимость, медицина, регенерация.

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