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Original paper

Tribological aspects of joint intraaricular therapy

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The condition of synovial joints affected by synovitis or degeneration dystrophy has been usually normalized by drugs of antibacterial, anti-inflammatory, immunomodulating and/or lubricating-protective action injected into the joint cavity. These preparations influence, but in different way, the friction in joints and wear of cartilages, even if they belong to the same pharmacological group and follow the same medication mechanism. With the development of a large group of lubricating-and-protective substitutes for the synovial fluid the tribological efficiency of injection drugs has begun to attract attention, whereas no information is available in the literature on pharmacopoeia or orthopedics about the lubricity of anti-inflammatory and antibacterial drugs commonly used as injections. The mechanisms by which structure and properties of lubricating films containing drugs undergo transformation under the influence of biological field in joints remain in fact unknown. In vitro experiments have been conducted to simulate a biofield of a joint; the lubricity of some injection drugs used in orthopedics has been evaluated.

Key words: *biophysical field, lubricity of drugs for injection, pendulum-type tribometer, coefficient of friction, tribological criterion for choosing drug*

1. Introduction

One of the most efficient methods of medicamental correction of the synovial medium of joints is injection of drugs into the joint cavity [1]. This approach is possible owing to developments in pharmacology – the development of drugs, of a wide range of effects, for injection [2]. Such drugs are administered after the etiology and pathogenesis of the disease have been ascertained in view of the patient's condition. In order to treat synovitis, antibacterial preparations and anti-inflammatory drugs based on glucocorticosteroids are injected into joints. To eliminate a pain the intramuscular injections of steroid-free preparations or analgesics are administered. To arrest the progressive deterioration of cartilage affected by degeneration-and-dystrophy, substitutes for synovial fluid (SF) – whose viscous film prevents the pathologically changed cartilages from contacting – are introduced into the joints [3]. The drugs injected into joint's cavity cause purposeful curing and being mixed with SF they change its biomechanical properties – lubricity first of all. Drugs of one pharmacological group acting by a similar curing mechanism can differently influence friction in joints, as well as wear kinetics of cartilagenous tissue. It was only after a large group of SF substitutes, some of them called *SF endoprostheses*, were adopted in clinical practice that the tribological efficiency of drugs, intended for injection into joints, has attracted some attention [4]. However, the literature on pharmacopoeia and arthrology lacks information about the lubricity of anti-inflammatory, antimicrobial, etc., drugs and analgesics commonly used in orthopedics [2].

Reliable data on drugs lubricity are difficult to obtain because, when a drug is in a joint, a lubricating film is formed in the biophysical field of the organism, and this field controls all processes in the joint's synovia. A proper physical field, biophysical field generated by a human body, is a fundamental notion

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of biophysics [5]. Numerous SF-generating processes occur in the biophysical field: blood dialysate filtering through the blood capillary walls into the synovial membrane (SM); biochemical combining of dialysate with the products secreted by SM cells; formation of complex protein–polysaccharide compounds of SF. The joint's biofield directly influences the physicochemical circulation processes of SF between the joint's cavity, microporous space of cartilagenous tissue and contact gaps in cartilages conjugated dynamically. The electromagnetic field (EMF) of a joint controls adsorptive formation of lipid layers for the cartilage boundary lubricant [6], as well as the properties of SF lubricating film which is responsible for liquid friction in a joint [7].

The weak EMFs of a human body (3–8 orders of magnitude lower than that of the Earth along with geomagnetic noises [5]) are generated by motions of electric charges within the body's tissues and magnetic colloidal particles suspended in biological fluids.

A great deal of information which undergoes exchange in a joint can only be transferred with the help of biological fluids because they, and even nerve impulses, are too "slow" to do such a work. An EMF simulation in a joint by in vitro experiment (i.e., within a controlled environment outside a living body) is an urgent task for medical physicists. The point is that the notion of biophysical fields in living bodies has been investigated in order to understand the nature of the higher nervous activities. This resulted in outstanding findings for which the Nobel Prize was awarded to: J.H. van't Hoff (Dutch), 1901, for discovering the laws of chemical dynamics and osmotic pressure; S.A. Arrhenius (Swedish), 1903, for his dissociation theory of ionization in electrolytes; W. Ostwald (German), 1909, for his work on catalysis, chemical equilibrium, the rate of chemical reactions, and electrochemistry; W. Nernst (German), 1920, for heat changes in chemical reactions and the third law of thermodynamics; Sir J.C. Eccles (Australian) for the transmission of nerve impulses; A.L. Hodgkin (British) and A.F. Huxley (British) for their description of the behaviour of nerve impulses (1963); I. Giaever (American), L. Esaki (Japanese) and B. Josephson (British) for the phenomena of electron "tunneling" through semiconductor and superconductor materials (1973). Their discoveries led to the development of the most sensitive magnetometer, SQuID*. The mechanisms of biophysical potential were understood and sensitive methods for medical diagnosis developed along with electrical and magnetic techniques for therapeutic treatment of numerous diseases. Unfortunately, the researchers did not pay any attention to the effect of the body's intrinsic EMF on the functioning of synovial joints. As a result, approaches to joint biofield simulation appeared underdeveloped, while the standard methods of tribological testing adopted in different countries [8] do not allow in vitro replication of the effect of a biophysical field on friction and lubrication of joints.

The present work was undertaken to advance an approach to simulating a natural EMF of a synovial joint; to conduct in vitro experiments and to evaluate the lubricity of the drugs to be injected into joints, and to compare them with biological lubricating fluids, i.e., SF and blood dialyzate.

2. Experimental procedure

The information on the tested drugs to be injected into joints is shown in the table. Their choice was made based on a distinct clinical effect, the results of their application in orthopedics, and availability.

Besides the drugs in the table, we tested other tribological correctors for joint's synovial medium (blood dialyzate-based preparations [9]−[14] belonging to a new class of pharmaceuticals). They are intended for replenishing the synovia deficit in "dry" joints, eliminating synovial pathologies (inflammatory, immune, viral, etc.), renewal of elements' interaction in joints by synovia circulation in their cavities [15]. Such preparations consist of drug-modified blood serum. This idea, i.e., biochemical and physicochemical verification of using the serum as a preparation for treating osteoarthritic joints, has been described elsewhere [16]. The intentional modification of blood serum of a patient (autoserum) by drugs which are unavailable as injections was carried out in patient's body. The patient was prescribed a definite drug; when its concentration was at maximum in the bloodstream, a blood sample was taken to be processed into serum. The procedure and the latest results of osteoarthritis treatment by injecting such preparations into joints are reported in another publication [17]. For comparison, the lubricity of healthy SF was evaluated. SF was considered relatively healthy if taken from somatically healthy patients who did not have traumatic or degenerated joints and whose SF-composition and properties were not damaged.

Blood serum and synovia were tested imposing the ethics regulations adopted at the 18-th (Helsinki, 1964) and 41-st (Hong Kong, 1989) World Medical Assemblies.

* SQuID – superconducting quantum interference device.

Table. Therapeutic drugs used for tribological tests

Drugs	Composition	Producer	Therapeutic effect
Hydrocortisone	Hydrocortisone acetate, 125 mg	Gedeon Richter (Hungary)	Anti-inflammatory
Kenalog-40	Triamcinolone acetonide, 40 mg; benzil alcohol, 9.9 mg	Bristol-Myers Squibb SpA (Italy)	
Diprospan	Betametasone dipropionate, 6.43 mg; betametasone sodium phosphate, 2.63 mg	Schering-Plau (Germany)	
Lincomycine hydrochloride	30% solution of lincomycine hydrochloride	Drug factory, Borisov (Belarus)	Antimicrobial
Chondrozamine	Chondroitine sulphate, 200 mg; glucosamine hydrochloride, 250 mg	Minskintercaps (Belarus)	A simulator for cartilage regeneration to take perorally
Synvisc	Hylan A and B, 8.0 mg in 1 cm^3	Biomatrix, Inc. (USA)	SF endoprosthesis
Hyalgan	Viscous solution of natural hyaluronic acid, 2 cm^3	Fidia Pharmaceuticals (Italy)	
Hya-Ject	Hyaluronic acid in physiological solution, 2 cm^3	ORMED GmbH & Co (Germany)	

The tests were run on the pendulum-type tribometer; the friction conditions in its support (slip-rolling friction) are close to the natural friction conditions in living joints. The tribometer has only one friction pair (the tested one), which ensures high accuracy and reproducibility of measurements (figure 1). The operating principle of the instrument is based on the estimation of the coefficient of friction from the recorded parameters of the pendulum decaying oscillations. The measuring accuracy is high, because a precise stress-frequency converter is used that allows estimating the area under the amplitude–time curve for a half-period of pendulum oscillations. The values of the parameters recorded are found by the computer processing of electric signals coming from the pendulum angle-sensing unit.

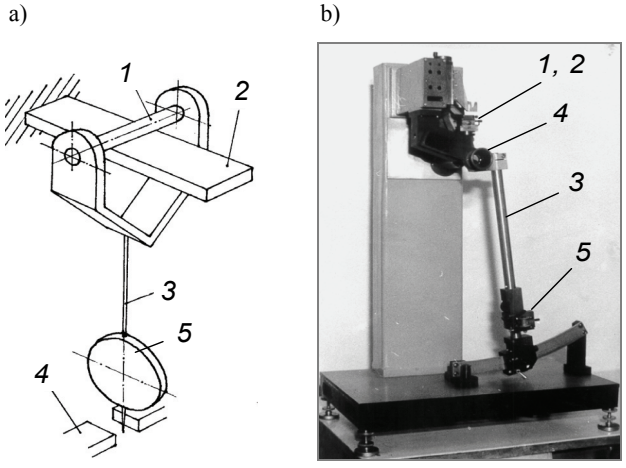

Fig. 1. Diagram (a) and general view (b) of the pendulum tribometer used to study friction in joints: 1 − indenter, 2 − sample, 3 − pendulum, 4 − oscillation counter, 5 − changeable weights

The friction pair of tribometer consists of a sliding base made from ultrahigh molecular weight polyethylene (UHMWPE), certified for orthopedic applications, and a triangular prism made from steel grade 12X18H9 to support the pendulum; the supporting edge of the prism is rounded to a radius r = 2.5 mm. The tests were run with a pendulum weight m = 2.0 kg at a sliding velocity v = 1.0 m/s, which corresponds to an average physiological stress on a human knee joint. A solenoid generates magnetic field in the friction zone of the pair under study (figure 2).

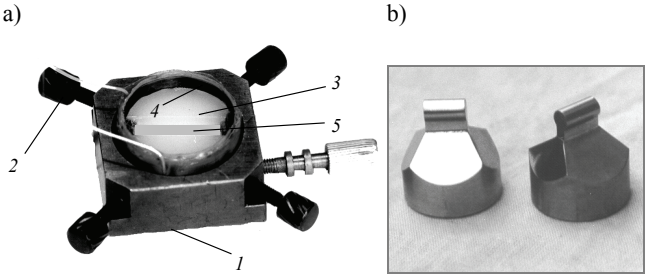

Fig. 2. Support (a) and indenters in the form of prisms (b): 1 − housing, 2 − screw, 3 − sliding base, 4 − solenoid, 5 − groove

The samples of SF or a drug were placed in the groove of the tribometer polymeric support and exposed to the electromagnetic field from the solenoid for 60 min. A direct current source was connected to the solenoid through a multimeter to generate magnetic field in the tribometer support. The tribometer sensors were connected to a digital measuring complex, which allowed automatic recording of the friction parameters. The values of the friction coefficient can be found from the following expression:

$$\mu = k\frac{28.147}{2\times 40\times n},$$

where:

k is the constant (k = 10) for the solenoid used;

n is the number of pendulum oscillations.

The fluid tested was syringe-injected into the sliding base groove; then the bearing edge of the prism was mounted into the groove.

To simulate a biophysical field in a joint, EMF parameters were chosen based on the following considerations. It is known that cartilages whose field vector is normal to the tribosurface are the source of biofield within the synovial joint [18]. The same is the direction − chosen for the EMF model.

Preliminary experiments showed that EMF of any direction influenced the friction in the SF-lubricated UHMWPE−metal pair. However, other conditions being equal, the lowest friction coefficient was recorded when EMF lines of magnetic force were normal to the tribosurface [19].

The influence of external EMF upon joints depends on the biotropic parameters of the field: intensity, gradient, vector, exposition, frequency, pulse shape, localization, and the area under effect. The combinations of these parameters lead to the following sequence of EMF biological activity: steady field < variable field < pulsed field [20].

A number of combinations of biotropic parameters of the external field and the dependence of joint response on the patient's general condition as well as magnetic susceptibility of joint tissues resulted in a dissimilar − often contradictory − empirical information about EMF arthrological effects. This proves that the theory of physicochemical effect of EMF upon friction and lubrication in joints is in the stage of accumulating experimental data that require systematization and generalization.

Hygienists are of the opinion that fields with magnetic induction above 0.2 μT [21] are harmful to human beings; nevertheless, steady, variable and pulsed fields with induction from 20–25 up to 40 mT have been applied to treat joints diseases [22].

To simulate the biophysical field of a human joint, a solenoid was used to generate a magnetic field; the solenoid was placed in the tribometer support and linked to a direct current source [23]. The induction on the friction surface was B = 10 mT. The sliding base was preliminary run-in during some starting 10 cycles of the unlubricated pendulum; as a result, the friction coefficient in the supporting system became stable.

3. Results

The results of tribological testing the drugs from the table are plotted in figure 3.

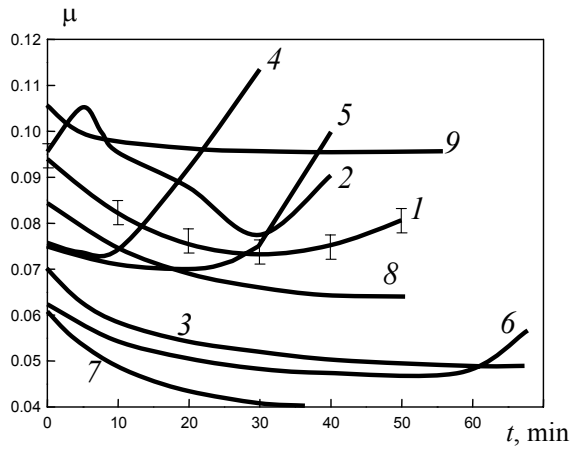

Fig. 3. Friction coefficient of pendulum tribometer support versus exposure time of a lubricating drug layer to solenoid field: 1 – hydrocortisone; 2 – Kenalog-40; 3 – Diprospan; 4 – lincomycine; 5 – Synvisk; 6 – Hyalgan, 7 – SF and serum, 8 – hydrocortisone + serum (1:1), 9 – chondrozamine. Confiding intervals shown in curve 1 are the same for all the curves

The drugs from different pharmacological groups showed different lubricating capacity and responded differently to the solenoid field:

- SF sampled from a comparatively healthy joint and blood serum of a relatively healthy patient showed the lowest coefficient of friction along with a marked decrease under the influence of the field (curve 7);
- the field affected the lubricity of hydrocortisone (1), Diprospan (3) and Hyalgan (6) in a way similar to that of healthy SF; μ markedly decreased with time immediately after the field was switched on;
- lincomycine (4), Synvisk (5) and Hyalgan (6) initially decreased the coefficient of friction under the influence of the field, but it rose with time;
- with Kenalog (2), μ varied in a non-monotonic manner following a general tendency to decrease;
- hydrocortisone combined with serum (8) showed an exponentially decreasing friction coefficient under the influence of field.

There is a distinct difference in the shape between curves 5 and 6 corresponding to Synvisk (5) and Hyalgan (6). Glucocorticosteroid-type preparations (Kenalog-40 and hydrocortisone) used as lubricants and showing a distinct anti-inflammatory effect

ambiguously influence the friction parameters. Hyalgan and Diprospan demonstrate the best lubricity of all the drugs tested.

The concentration dependences of μ in the case of tribometer support lubricated with a mix of serum + hyaluronic substitute of SF are within the range from 0.07 to 0.04. They suffer minimum (μ = 0.04) at the concentration for Synvisk = 50%, Hyalgan = 75%, and Hya-Ject = 75%.

The kinetic dependences of μ-variations in the solenoid field were obtained when the tribometer bearing plate was lubricated with blood serum taken from a viral osteoarthritic patient (figure 4). Three samples of autoserum were tested: 1 – initial condition; 2 – one hour passed after the patient had taken 100 mg of Doxycicline – an antibiotic drug of the tetracycline group; 3 – a week after the drug had been administered and one hour after the patient had taken 200 mg of Doxycicline.

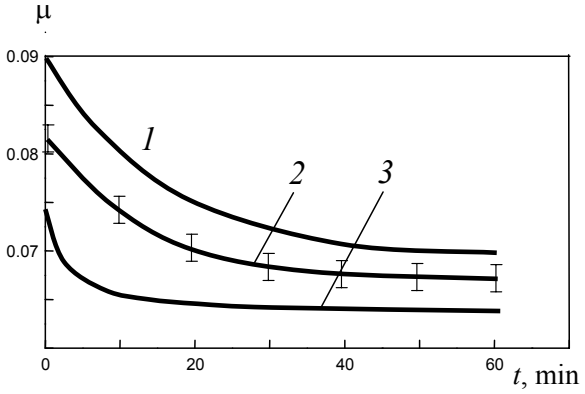

Fig. 4. Friction coefficient of the tribometer support versus time during which the solenoid field was acting upon the blood autoserum (explanation is given in the text)

4. Discussion

The results presented graphically in figure 3 are indicative of the following. The difference in lubricity between hyaluronic substitutes for SF (curves 5 and 6) arises, obviously, from their different viscosities and wetting of the tribometer sliding elements. Synvisk is a jelly-like substance with dynamic viscosity η = 30 Pa·s [24] that poorly spreads over the bearing surface during sliding. Hyalgan has a lower viscosity (η = 15÷20 Pa·s [25]) and wets better the UHMWPE element leading to the lowest friction coefficient of all the drugs tested. The mentioned property of Synvisk has been emphasized in all papers which describe its clinical effect: the contact between the damaged cartilage spots is averted and they are not traumatized under high mechanical stresses owing to high elasticity and supporting power of the lubricating layer [3], [4].

The glucocorticosteroid-type drugs – Kenalog-40 and hydrocortisone – show a distinct anti-inflammatory effect, and they substantially impair friction parameters of the tribometer support (curves 1 and 2). It is observed that these drugs suffer phase separation which starts at the moment of taking away from ampoules. The higher friction coefficient was produced by hydrocortisone which is characterized by precipitation of the crystalline sediment deposited on the tribosurface; besides, the liquid phase is expelled from the sliding base by pendulum oscillations. As a result of these events, the lubricating layer in the tribometer clearance mostly consists of crystalline hydrocortisone acting like an abrasive matter. A similar picture was observed for Kenalog-lubricated friction. Diprospan is a more stable suspension of colloidal particles, which imparts favourable tribological qualities of this drug. Serum-diluted hydrocortisone (curve 8) markedly reduces the friction coefficient in the tribometer sliding pair. Such preparations can be injected into human joint cavities without serious consequences and without damaging the cartilage by the crystalline phase of hydrocortisone [14].

Lincomycine hydrochloride (4) used for treating infective-inflammatory processes is a salt solution which undergoes crystallization during friction in air. However, the water-soluble crystalline phase is less abrasive for cartilages, especially if mixed with SF in a joint.

So, Hyalgan (6) and Diprospan (3) show the best lubricity of all the drugs studied. When used as lubricants in a model friction pair, these drugs act like healthy SF, i.e., they ensure quite low friction coefficients whose magnitude decreases under the influence of the field. Probably these drugs form – in a lubricating layer – three-dimensional molecular complexes similar to protein–polysaccharide complexes of SF [26] that are formed from structurally coordinated and functionally related components.

An increase of friction coefficient with time in tribometer support under lubrication of Synvisk and Hyalgan (5, 6) can be explained by tribodestruction of hyaluronic chains, lowering of lubricant viscosity and load-carrying capacity of lubricating layer.

A 9% chondrozamine water solutions (figure 3, curve 9) only slightly respond to the solenoid's field and have poor lubricity: the friction coefficient value – for the solution-lubricated pendulum sliding base – is one of the highest (μ = 0.095). This drug, if taken in the form of capsules, shows a clinical effect after

a considerably long time (about 6 months). The experiments showed that chondroitine preparations introduced into joints disorganize the cartilage structure and accelerate its destruction [27]. Therefore, Chondrozamine seems advisable for intraarticular injections.

Hyaluronates play an important part in the provision of load-carrying capacity of lubricating layer by the regulation of SF viscosity. Dynamic viscosities η of SF taken from health joint and from joint with synovitis where depolymerisation hyaluronates process takes place are equal to $(4.8\pm3.7)\cdot10^{-3}$ Pa·s and $(3.6\pm2.7)\cdot10^{-3}$ Pa·s, respectively. This SF cannot fulfil in full measure the functions of lubricant, shock-absorber and cartilage protector. Viscosity of blood is $3\cdot10^{-3}$ Pa·s and blood serum is still lower ~ $1.8\cdot10^{-3}$ Pa·s [28]. Therefore, serum as preparation for injection to joints should be modified by hyaluronates.

The mixes of serum with hyaluronic substitute for SF are efficient lubricating materials with serum concentration (C) that gives maxima in $\mu(C)$ relationship. We believe that the complex compounds of proteins, polysaccharides and hyaluronates – similar to healthy SF structures – are formed in the lubricating layer under the sliding conditions and field. Evidently the minima correspond to hyaluronate maximum concentration at which all hyaluronate molecules get included into the structure of such compounds. These minima are typical of injection preparations based on serum that favourably combines the concentrations of Synvisk [13], Hualgan and Hya-Ject [11], as well as the hyaloid preparation used for corpus vitreum [12], being protected by patents. Clinical testing proved their positive activity in curing osteoarthritic joints [29].

An analysis of data plotted in figure 4 showed that:

- all of the lubricating liquids tested contain, as a base, patient's blood autoserum whose magnetic susceptibility allows the friction coefficient to decrease under an external EMF;
- the autoserums tested have dissimilar lubricities; the approximate differences in the initial values of friction coefficient (μ_0) are 0.01;
- combination of Doxycycline with blood proteins in a patient's body enhances the autoserum lubricity.

The latter finding can be explained by the fact that active Doxycycline molecules – when in the patient's bloodstream – enter the serum protein phase and improve its lubricity. As a boundary type of lubrication is carried out in the pendulum support, it seems possible that μ_0 decreases thanks to increased adsorption activity of the modified serum. Therefore, the therapeutic effect of such injections not only results from the purposeful action of Doxycycline, which stops the spread of microorganisms, inhibits destructive enzymes in joints, and improves cartilage nourishment with serum protein compounds, but also from its better lubricity, hence, from tribological condition of the joint.

A technique described in [16] allowed the expediency of drug injection into joints to be estimated; the technique was developed in terms of the tribological criterion. That drug is better whose friction coefficient μ_0 is equal to or lower than μ_0 for pathological SF sampled from a patient's affected joint, as measured before switching the field on. That is why, anti-inflammatory steroids showing wide variations in μ because of phase separation are advisable if alternative preparations are unavailable. The abrasiveness of separating drugs can be reduced by mixing them with autoserum or donor's serum of the patient's blood group [30]. In any case, if crystallizable drugs are injected, a mild orthopedic regimen should be advised (e.g., joint's immobilization, limited loading) until the crystalline phase has completely dissolved in SF.

With μ_0 of drug > μ_0 of SF, the dynamics of friction coefficient reduction in the tribometer support under solenoid's EMF should be estimated. If the lowest μ-value reaches μ_0 of SF of the patient, this drug is advisable for injections with a simultaneous magnetotherapy of the joint.

SF substitutes can be administered after the SF-biomechanical resources have been consumed; poor lubricity and lack of sensitivity to an external EMF are indicative of such situations.

Only the joints generating biological friction are capable of compensating cartilage wear and restoring the worn areas on tribosurfaces by the regeneration of cartilagenous tissue. This important quality of biomaterials made a basis for transfusal chondroprotection, a method of tribological correction of osteoarthritic joints, using serum containing drugs of anti-inflammatory, antimicrobial, and immunosimulating actions. Serum modified naturally with a certain drug in the blood stream of a patient, to whom this substance is administered perorally or intramuscularly, appeares to be a highly efficient means for treating osteoarthrites because it is prepared individually for every patient [17].

5. Conclusions

The pendulum-type tribometer simulating biophysical field of joint was used to test drugs to be injected into joints. It has been established that irre-

spective of pharmacological group, each of the drugs tested has its own lubricity. Other conditions being equal, a drug with the best lubricity is most advisable for injection.

The technique for tribological testing of drugs has been applied to develop preparations for osteoarthritis. The preparations are based on blood serum sensitive to EMF and having the best lubricity of all biological fluids. Autoserum-based preparations are developed from patient's blood which is naturally saturated with purposeful drugs (anti-inflammatory, antimicrobial, immunomodulating) administered in advance either perorally or intramuscularly. This drug-marking method has the merit of introducing serum into joint together with drugs unavailable in the injection form. The injection-type drugs are mixed with donor's serum in a syringe before being injected into the joint. The results of the in vitro tribological testing of the developed preparations have been verified during clinical test of the transfusive chondroprotection technique at medical institutions of Belarus.

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