DOI 10.1007/s11094-021-02541-7
Pharmaceutical Chemistry Journal, Vol. 55, No. 10, January, 2022 (Russian Original Vol. 55, No. 10, October, 2021)

DRUG SYNTHESIS METHODS AND MANUFACTURING TECHNOLOGY

PROSPECTS OF A TRANSDERMAL DOSAGE FORM (MICRONEEDLES) AND JUSTIFICATION OF THE ACTIVE SUBSTANCE SELECTION FOR DEVELOPMENT OF A NEW MEDICINE

U. V. Nogaeva,[1,*] A. A. Leshkevich,[1] D. S. Yurochkin,[1] Z. M. Golant,[1] E. V. Flisyuk,[1] and D. Yu. Ivkin[1]

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 55, No. 10, pp. 23 – 34, October, 2021.

Original article submitted July 29, 2021.

Prospects for the development of a transdermal dosage form (DF) based on microneedles were considered. Methods for obtaining such systems, the application areas, and data from the pharmaceutical market were examined. A wide sample of INNs that are used to reduce pain in osteoarthritis patients was formed based on clinical guidelines. The market capacity, sales by Anatomical Therapeutic Chemical (ATC-2) groups, and sales depending on the DF were discussed. Criteria for the choice of active ingredients with market potential were defined. An analysis of a short list revealed that meloxicam has sufficient market potential to create a microneedle DF. A forecast of meloxicam consumption based on time series models indicated stable sales-growth dynamics and a potential market size of 4.6 billion Russian rubles by 2030. Results of the study indicated good market prospects and justification of pharmaceutical development of a new transdermal DF including meloxicam microneedles as the active ingredient.

Keywords: transdermal dosage forms, microneedles, meloxicam, osteoarthritis, market analysis.

Transdermal administration of active pharmaceutical ingredients is the safest alternate use of parenteral and peroral dosage forms (DFs) for both patients and animals. Topical forms enjoy significant advantages including:

–avoidance of primary metabolism of active ingredients in the liver and enzymatic degradation;

–reduction of systemic side effects from drug administration such as adverse reactions in the gastrointestinal tract;

–simple and painless administration.

Transdermal transport of medicines has its limitations. For example, few active ingredients have the particle size and physicochemical characteristics necessary to penetrate the skin, in particular the stratum corneum. Therefore, pharmaceutical companies and scientific research institutes applied significant efforts in this direction to develop compounds enhancing the permeability of the dermal barrier [1] and to elaborate iontophoresis and electroporation methods [2 – 4]. Microneedle systems were developed considering patient demands to increase the convenience of administration and efficiency of transdermal drug delivery [5].

The goals of the present research were to study the technological specifics of the novel transdermal form, i.e., microneedles; to examine possible areas of microneedle application in clinical practice; and to justify the selection of active ingredient for subsequent development of a finished dosage form (microneedles) based on an analysis of the pharmaceutical market.

The following issues were resolved during the research:

[1] St. Petersburg State Chemical and Pharmaceutical University, Ministry of Health of the Russian Federation, 14/A Prof. Popova St., St. Petersburg, 197376 Russia.
[*] e-mail: uljana.nogaeva@pharminnotech.com

1. The technological specifics of the novel transdermal DF (microneedles) were studied;

2. The clinical efficacy was assessed and promising niches for medicines were revealed;

3. The selection of a disease and an INN used for its therapy was justified;

4. The market potential of the novel DF was analyzed and evaluated. The sales volume upon entry into the market of the novel microneedle DF was predicted.

EXPERIMENTAL PART

Currently existing information on microneedle DFs and experience with their use was studied and generalized by analyzing clinical trial data during the work. This enabled the therapeutic efficacy of such DFs to be assessed. The clinical data were studied using the Cochrane library [6].

Market research was performed to select potential sectors and active ingredients with market potential in the microneedle DF. Pharmaceutical market data were collected and analyzed using the DSM Group analytical database [7]. Market research used segmentation according to finance sources, i.e., commercial and hospital sectors including a study of drug release through subsidized drug supply programs.

The market research study included the following stages:

1. An evaluation of existing clinical data and the identification of promising medicine groups.

2. A determination of pharmaceutical market sectors (indications for use) in which the studied groups of active ingredients are used.

3. Formation and analysis of sales of a wide set of active ingredients used for the investigated indications and holding potential for adaptation as a microneedle DF.

4. Development of criteria that active ingredients with great potential on the Russian pharmaceutical market should meet.

5. Selection of an active ingredient meeting to the compiled criteria.

6. Evaluation and prediction of the market volumes of the microneedle DF of the medicine.

RESULTS AND DISCUSSION

Microneedles form a system with a diameter from tens to hundreds and a length from hundreds to thousands of micrometers and are intended for minimally invasive cutaneous administration of medicines and cosmetics.

The main operating principle of microneedles consists of disturbing the stratum corneum and creating micron-sized pathways through which a drug enters the epidermis or the upper dermal layer. Such systems do not affect blood vessels and nerve endings and are not painful because of their micrometer dimensions. Several varieties of microneedles are distinguished depending on the structure and mechanism of action:

1. Monolithic microneedles are spikes that are usually deposited on a roller. They pierce the stratum corneum, opening access to echinate, smooth, and grainy layers. Then, a topical DF, e.g., ointment, gel, cream, etc., is placed on the skin surface.

2. Hollow microneedles can introduce an active ingredient into the basal layer and deeper. A drug is fed through the inner needle channel to the intended site. Such microneedles are most conveniently used in handheld devices.

3. Soluble microneedles consist of a compressed active ingredient or polymer with a drug that dissolves directly in tissues over time.

4. “Sweating” microneedles are structurally similar to soluble ones and contain the active ingredient at a higher concentration. The active pharmaceutical ingredient (API) is released after a hydrogel is formed by liquid from the intercellular space permeating into the needle [8].

Microneedles can be produced by several technologies. A method where a solution of a biologically soluble polymer is poured into a previously fashioned form and centrifuged or pumped under vacuum so that the polymer fills all microcavities is most often used. The solvent is evaporated, resulting in the formation of solid microstructures.

New methods began to be developed at the start of the 2010s. A method of polymer lithography according to which a polymer heated to the glass transition temperature was placed on a plate and stretched slowly during solidification to form characteristic conical microneedles was reported. This method has several limitations because high temperatures are used. For example, thermally labile APIs and protein drugs cannot be incorporated into the polymer matrix.

Additive technologies utilize 3D printing to produce microneedles. Computer design can create systems of various shapes and sizes. As a rule, photolithography from various types of epoxy resins and fused deposition modeling (FDM) 3D printing are used for this. Photolithography can reach high accuracy although it is limited by the used materials and the capability to produce biodegradable systems. Microneedles produced by FDM printing sometimes need postprocessing. Also, the polymer is subjected to thermal effects that limit the incorporation of several APIs into the DF.

Medicines in microneedle DFs are currently absent in the State Drug Registry of the Russian Federation. Thus, the microneedle DF is innovative for the Russian pharmaceutical market. Patches with microneedles of the third and fourth types can now be manufactured at scientific subdivisions of St. Petersburg State Chemical and Pharmaceutical University using master forms.

Evaluation of clinical data and identification of promising drug groups

Results of clinical trials (CTs) of medicines in microneedle DFs were searched and the main advantages

and clinical efficacy of such DFs were evaluated to justify their development. An analysis of CT data showed that drugs in microneedle DFs could be used in several applications.

1. Pain from use of microneedles and evaluation of microscopic wound healing

Specialists of the University of Cardiff investigated pain from the use of microneedles as compared to subcutaneous (s.c.) injections [9]. The study included 12 patients that received a single s.c. injection using a 25G needle and two sets of microneedles (36 needles of height 180 and 280 μm). The pain intensity was evaluated using a visual scale. Sensory perception was determined by an adapted short form of a McGill questionnaire. Skin penetration was determined by external staining and measurement of transdermal fluid loss. The average scores on the visual scale and the questionnaire results showed that the microneedles caused significantly less pain and discomfort in the participants than s.c. injections. Staining with methylene blue and analysis of fluid loss confirmed that micropores were formed in the skin by applying the microneedles and closed within 8 – 24 h after application. This study demonstrated the potential of microneedles with respect to skin penetration with minimal pain and discomfort by creating transitory delivery pathways for drugs, vaccines, and DNA.

2. Use of microneedles for vaccination

A randomized partially blinded placebo-controlled phase I CT at Emory University (USA) involved 100 healthy patients 18 – 49 years old [10]. The participants were divided into four groups, i.e., those receiving intramuscular (i.m.) injections of inactivated influenza vaccines, receiving microneedle injections of vaccine from medical personnel, using microneedles for self-vaccination, and a placebo group.

Significant differences in the frequency of adverse effects among the groups were not found in the study results. Elevated sensitivity and pain at the injection site occurred in 60 and 44% of cases in the group with i.m. injections. Elevated sensitivity (66%), erythema (40%), and irritation (82%) were noted after microneedle administration. The average antibody titers were similar in groups with i.m. injections and microneedles. The percent seroconversion was significantly higher in the microneedle group as compared to the placebo.

Debriefing of patients about the study results showed that 98.6% of patients in the microneedle group reported a positive vaccination experience as compared to 86.4% of those with i.m. injections [11]. With respect to future injections, 65 of 99 patients completing the questionnaire preferred microneedles. The advantage of microneedles for convenience of administration and efficiency of self-vaccination was noted.

3. Use of microneedles for administering insulin

An investigation at Emory University (USA) included 16 participants of childhood and adolescent age with type 1 diabetes [12]. The aim of the work was to assess the potential of microneedles for increasing compliance of immature patients because of the reduced pain after replacing insulin injections using catheter-pumps. It was found that pain was significantly less if microneedles were used. The onset of insulin lispro action was 22 min faster in the microneedle group than in the catheter-pump group.

Studies at V. I. Shumakov Federal Scientific Center of Transplantology and Artificial Organs, Ministry of Health of Russia, showed the possibility in principle of increasing the diffusion rate of insulin through the skin *in vitro* with preliminary application to it of microneedles [13].

4. Microneedles in cosmetology

Modern cosmetology avidly uses the latest scientific achievements from the medical sector. Two large plants now manufacture biologically soluble microneedles for cosmetology. One is located in Korea; the other, in Russia. A study conducted in 2017 involving 34 females showed that a patch with microneedles containing hyaluronic acid was more effective for smoothing wrinkles than a lotion of analogous composition. Also, the procedure was painless and did not irritate skin [14].

Patches with hyaluronic acid were placed on the outer corner of the right and left eye and a defined area of the palmar forearm of healthy subjects with aged skin in a multicenter 12-week clinical trial. Instrumental analysis of the skin properties showed that the number of wrinkles decreased by 25.8%, skin hydration rose by 15.4%, and dermal skin density and thickness increased by 14.2 and 12.9%, respectively [15].

5. Microneedles as DFs for delivery of analgesics

Researchers at Georgia Institute of Technology (USA) conducted a randomized blind CT involving 15 patients to reveal the potential of using microneedles for local anesthesia by lidocaine as judged from the effectiveness of anesthesia and pain reduction as compared to s.c. injections [16]. Pain from administration was evaluated on a visual scale. The results of the pain evaluation showed a reduction of pain from administration of microneedles and no significant difference in the strength and area of local anesthesia between the microneedles and s.c. injections. A total of 77% of the patients preferred microneedles over injections while 80% thought that microneedles caused no pain.

It is noteworthy that the ability of microneedles to increase skin permeability for NSAIDs [17] was confirmed in experiments on *in vitro* diffusion on split skin of cattle [18, 19].

Thus, CT data showed that the microneedle DF could potentially reach an effectiveness comparable to s.c. and i.m. injections of several drug groups and had advantages with re-

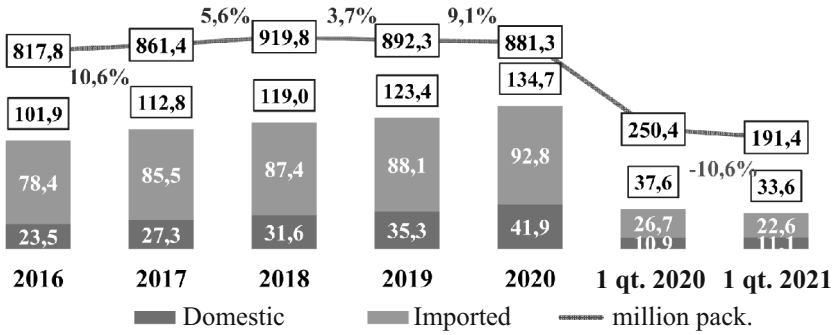

Fig. 1. Market volume of drug set in monetary and natural units from 2016 to the 1st quarter of 2021, billion RuR (retail prices); million packages.

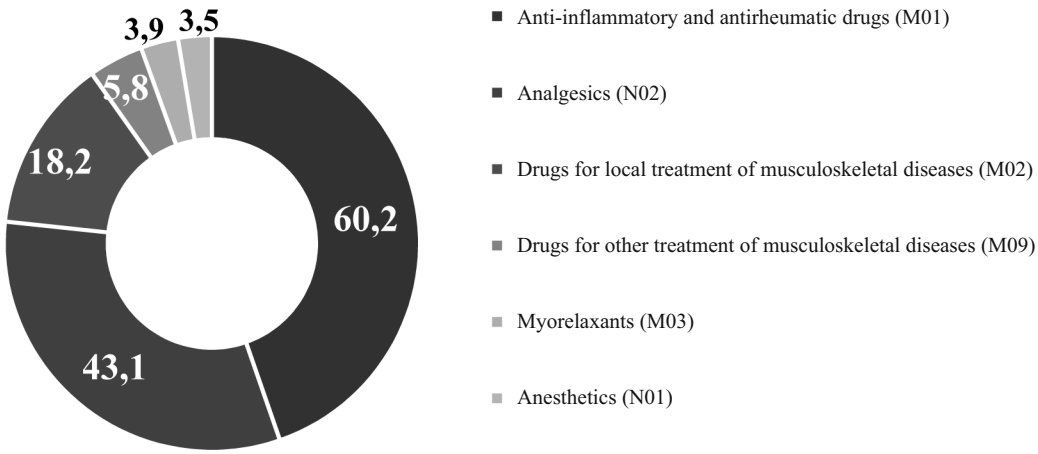

Fig. 2. Sales of drug set by ATC-2 groups in 2020, billion RuR (retail prices).

spect to end-user properties (pain reduction, convenience of self-administration). This DF was promising for developing children's medicines.

Justification of disease choice

CT data are indicative of the potential effectiveness of vaccines, insulin, and analgesics in the microneedle DF. Analgesics represent a high-priority drug class for which the labor-intensiveness and duration of development are acceptable from a short-term perspective. Their use in microneedles presupposes external application and the lack of systemic effects. Musculoskeletal system diseases that are combined into ICD class XIII and are globally considered one of the most common pathologies of modern society are the main indication for use of such drugs. Pathology of joint synovium, i.e., osteoarthritis (ICD-10: M15-M19 Arthritis), which is one of the major causes of invalidism in the geriatric population, is one of the most important pathologies.

Osteoarthritis (OA) is a heterogeneous disease group of various etiologies with similar biological, morphological, and clinical manifestations and outcomes that involves all joint components, primarily cartilage and subchondral bone, the synovial sac, ligaments, capsules, and periarticular muscles [20].

OA has an incidence of 6.43% in the population. It correlates with age and reaches a maximum of 13.9% in people older than 45 years [21, 22]. However, the incidence of OA in the population could be up to 25% according to research results [23]. OA occurred in 23.6% of cases in older adults in the RF among all patients with ICD-10 class XIII diseases in 2011 and 25.8% in 2016 [24]. According to healthcare statistics, 20% of the global population suffers from OA. This is 25 million people in Russia (17.3% of all Russians).

Contemporary approaches to treating OA are symptomatic methods aimed at relieving pain and improving musculoskeletal functioning. However, the therapeutic effect from using them is limited so that greater than half of OA patients cannot achieve adequate relief.

Many issues with therapeutic strategy remain unresolved, despite many recommendations for treating OA being published from 2003 to 2014 by the Association of Russian Rheumatologists [20], the European Alliance of Associ-

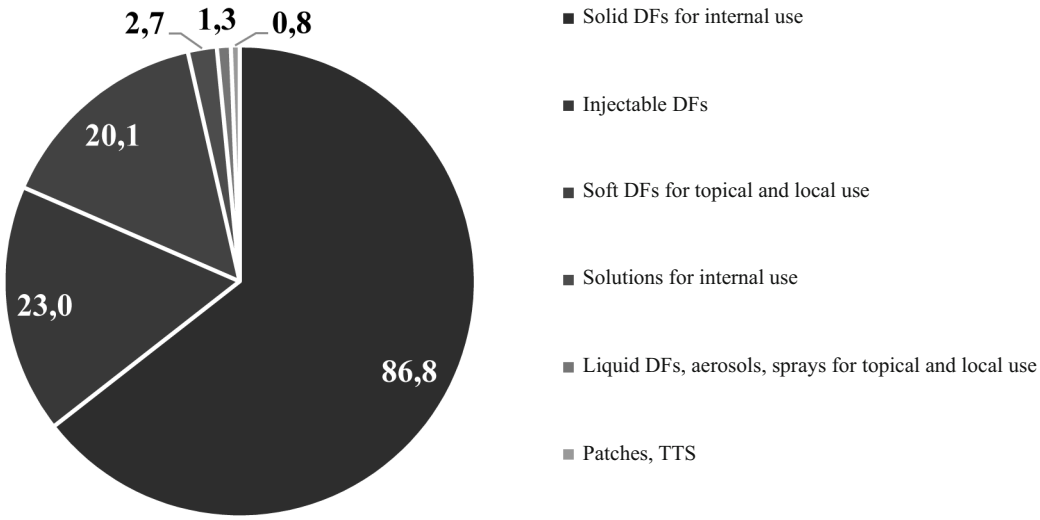

Fig. 3. Sales of drug set by administration mode and dosage forms in 2020, billion RuR (retail prices).

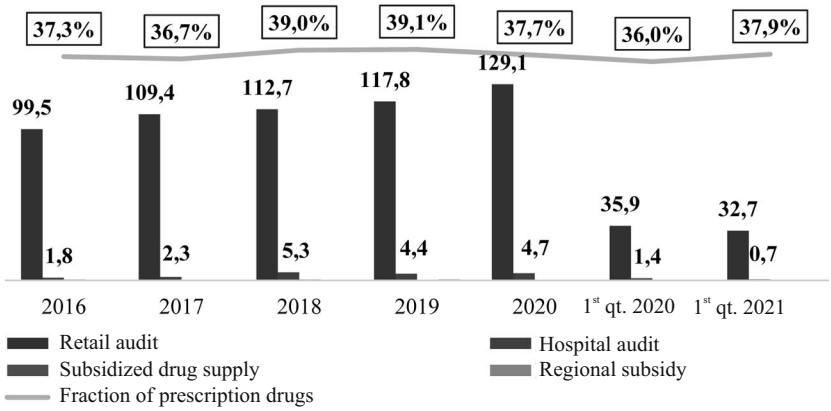

Fig. 4. Market volume of drug set by Russian pharmaceutical market sectors in monetary units from 2016 to the 1st quarter of 2021, billion RuR (retail prices).

ations for Rheumatology (EULAR) [25], the American College of Rheumatology [26], the National Institute for Health and Care Excellence of Great Britain (NICE) [27], and the Osteoarthritis Research Society International (OARSI) [28].

For example, the World Health Organization (WHO) confirmed that research on the cost-effectiveness, safety, and efficacy of long-term OA management with currently accessible pharmaceutical therapies is critical [29].

According to the report *Opportunity Analyzer: Osteoarthritis and Forecasts to 2026* [30], the OA market is expected to grow from $1.6B in 2016 to $3.5B by 2026 in the seven main markets (USA; the EU countries France, Germany, Italy, Spain, and Great Britain; Japan) with a compound annual growth rate (CAGR) of 8.1%.

The research showed that the market growth rates can be attributed to an increased number of elderly and introduction to the market of new biologic analgesics with a higher anticipated annual cost of therapy. Currently, new types of OA pharmaceutical therapies are being aggressively developed by pharmaceutical companies owing to an improved pathophysiological understanding of the disease. The research and development strategy for OA is characterized by a tendency to develop new analgesics and NSAIDs, including novel DFs.

Thus, the development of novel DFs for symptomatic treatment of OA is a challenging problem, the solution of which could be the emergence onto the market of NSAID microneedle DFs as a unique application for patients with pain syndromes. Also, such medicines could be used for general symptomatic therapy of pain syndrome from rheumatoid arthritis, bruising, dislocations, and muscle tears.

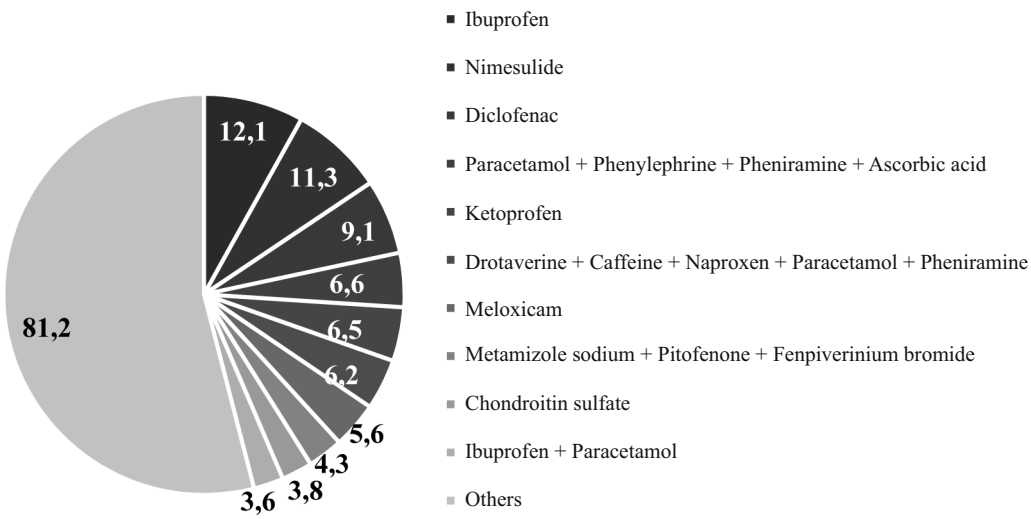

Fig. 5. Top-10 INN set by drug sales in 2020, billion RuR (retail prices).

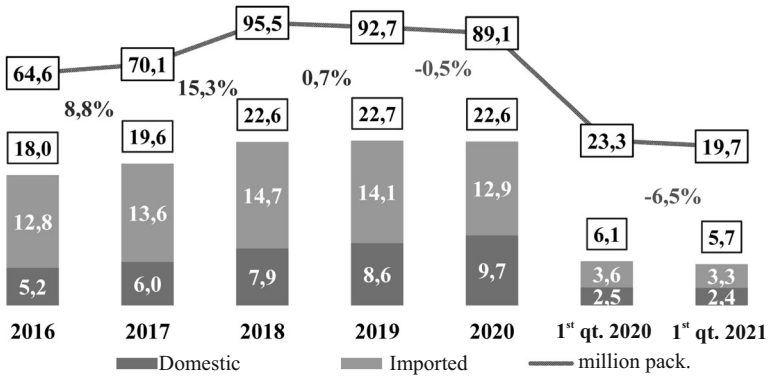

Fig. 6. Market volume of short list in monetary and natural units from 2016 to the 1st quarter of 2021, billion RuR (retail prices), million pack.

Formation of a set for market analysis

According to clinical recommendations for diagnosis and treatment of OA [31], the following drug groups are used as symptomatic therapy of OA pain syndrome:

- analgesics;
- NSAIDs (peroral and transdermal DFs);
- glucocorticosteroids;
- chondroitin, glucosamine, hyaluronic acid, Piascledine.

Highly active pharmaceutical glucocorticosteroids were excluded in the set formation stage because strict requirements are imposed on their manufacturing process. For example, isolated manufacturing rooms with a maximum allowed weighted average concentration below 10 μg/m^3 of air are required for classification to classes OEB 4 and OEB 5. Also, Piascledine formulations that have no evidence-based efficacy as transdermal or injectable DFs were excluded.

Thus, a broad set for research on the market potential included the drug groups analgesics, NSAIDs, chondroitin, glucosamine, hyaluronic acid, and their combinations as satisfying acceptance criteria in clinical practice with combined therapy of OA and the existence of external/injectable DFs of these groups.

Analysis and study of the market potential of the set

The broad set included 158 international nonproprietary names (henceforth INNs) used to ameliorate OA pain syndrome, among which the main fraction were NSAIDs and their combinations.

The total sales of drugs in the set were 134.7 billion RuR in 2020, showing 9.1% growth (Fig. 1). The market volume of the drugs in natural units was 881.3 million packages, which was 1.2% less than in 2019. The average annual growth rates of revenue and natural sales for the last five years were 7.2 and 1.9%, respectively.

Sales for the first quarter of 2021 were 33.6 billion RuR and 191.4 million packages, which were reduced by 10.6 and

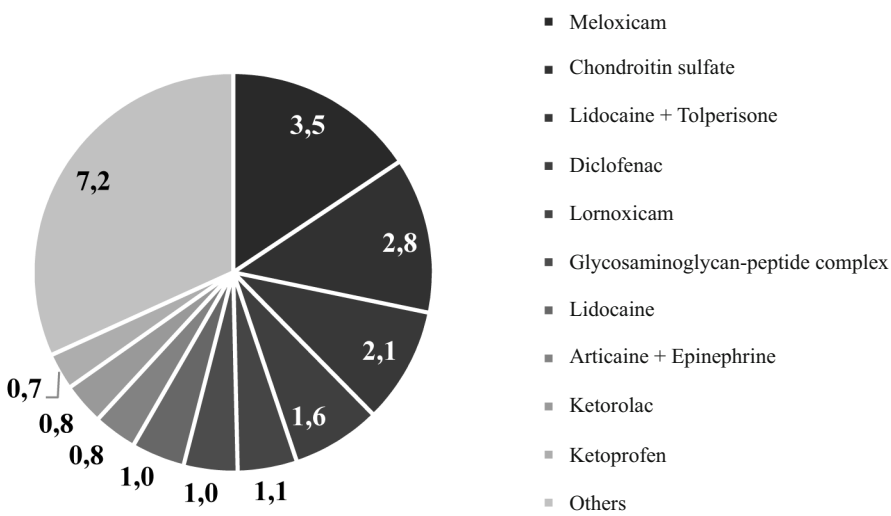

Fig. 7. Top-10 INN by sales of short list of drugs in 2020, billion RuR (retail prices).

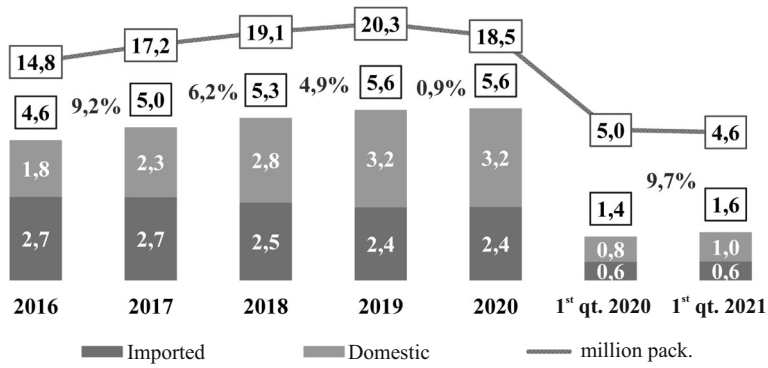

Fig. 8. Market volume of INN meloxicam in monetary and natural units from 2016 to the 1st quarter of 2021, billion RuR (retail prices), million pack.

23.6%, respectively, relative to the analogous period of 2020. A large part of the revenue came from imported drugs.

The set comprised drugs from six groups of ATC classification level 2. Of these, two groups accounted for 60% of the market in monetary and natural units in 2020, i.e., M01 and N02 (Fig. 2).

Group N02 showed 14.6% growth in monetary and 1.5% drop in natural units relative to 2019. M01 drugs grew by 10.0 and 1.3% in monetary and natural units, respectively.

Solid DFs for internal use (tablets, capsules, powders, granules) covered >50% of the market in monetary and natural units (86.8 billion RuR and 664.9 million pack.) as compared to 2019. Their market increased by 13.5 and 0.3%, respectively (Fig. 3).

Injectable DFs were the second group by volume at 23.0 billion RuR and 86.7 million packages, dropping by 1.6% and 4.1% in monetary and natural units, respectively, relative to 2019.

Figure 4 shows that the key market sector of the drug set was the commercial sector with >90% in monetary and natural units in 2020 at 129.1 billion RuR (+9.6%) and 841.4 million pack. (–0.1%). Sales dropped in 2021 relative to the first quarter of 2020. However, this was probably due to increased demand in 2020 during spread of a new coronavirus infection (COVID-19).

The fraction of prescription drugs was stable for the last five years in the range 37 – 39% in monetary and 22 – 27% in natural units.

The greatest fraction of revenue in the set in 2020 came from INNs ibuprofen and nimesulide at 12.1 billion RuR (+4.2%) and 11.3 billion RuR (+14.5%), respectively (Fig. 5). INN ibuprofen + paracetamol had the greatest growth in the top 10 (35.5%). Revenue decreased only for INN chondroitin sulfate (–3.8%).

Thus, the set of analgesics used for OA in the RF amounted to 134.7 billion RuR of pharmaceutical market sales and showed stable growth for the last five years. A

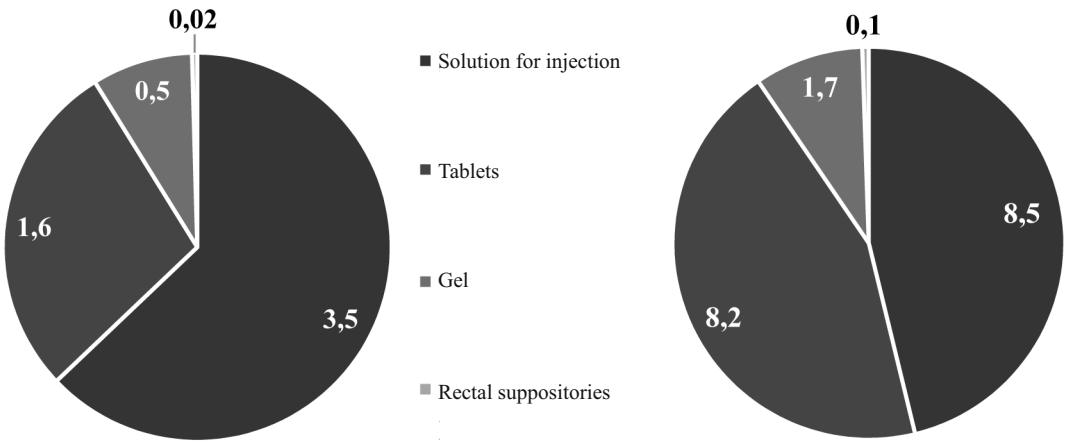

Fig. 9. Sales of INN meloxicam by dosage forms in 2020, billion RuR (retail prices, left), million pack. (right).

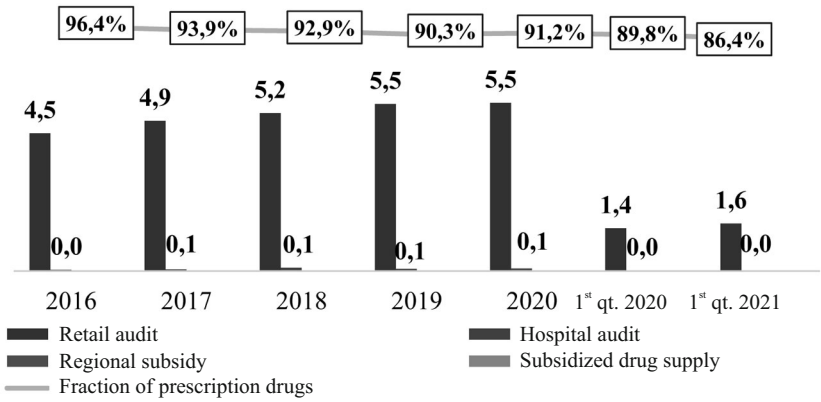

Fig. 10. Market volume of INN meloxicam by Russian pharmaceutical market sectors from 2016 to the 1st quarter of 2021, billion RuR (retail prices).

large part of revenue (68.9%) came from imported drugs. Foreign drugs made up 38.9% of the demand in natural units. Solid DFs for internal use were the market leaders.

The following criteria for choosing the active ingredient for creating a microneedle DF could be formulated based on sales data and CT results:

1) Clinical data indicate microneedles have advantageous end-user characteristics relative to injectable DFs and analogous efficacy. The active ingredient should have a large market share of injectables. The microneedle DF could potentially replace other external DFs (gels, ointments, creams, etc.).

2) The active ingredient should belong to ATC-2 group N01 or M02.

3) The active ingredient should be sold primarily in the commercial market sector.

These criteria enabled the formulation of a short list including injectable DFs, analgesic patches, and transdermal therapeutic systems.

Market analysis of short list

The short list included 38 INNs, the market volume of which was 16.8% in monetary and 10.1% in natural units of the broad set. The short list in 2016 – 2020 showed growth of 4.6 billion RuR. A large part of the market increase came from locally manufactured drugs. The natural growth during this period (24.5 million pack.) also came from domestic drugs (Fig. 6).

Sales in the first quarter of 2021 dropped in monetary and natural units by 6.5 and 14.5%, respectively. This was probably associated with deferred demand resulting from the epidemic of the new coronavirus infection.

The commercial sector was a key market segment. Its volume increased by an average of 0.6 billion RuR and 1.4 million pack. per year for the last five years. The demand from the government sector was characteristically unstable and decreased gradually after an increase in 2018.

Meloxicam was the leader in the top 10 INN injectable and transdermal drugs with a 15.6% fraction and an increase of 0.8% in 2020 vs. 2019 (Fig. 7).

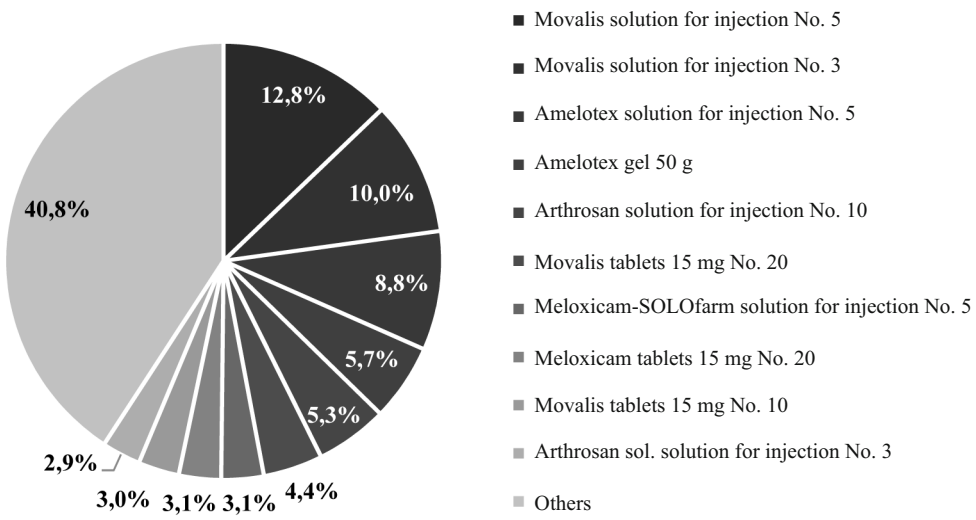

Fig. 11. Distribution of market fractions of top-10 by SKU INN meloxicam by sales in 2020 in monetary units.

Fig. 12. Sales of INN meloxicam by federal districts in 2020, billion RuR.

An analysis of the short list of injectables, analgesic patches, and transdermal therapeutic systems showed that INN meloxicam had a market advantage. Sales were studied to determine if meloxicam met the established criteria.

Market analysis of selected INN meloxicam

The market share of INN meloxicam in 2020 was 5.6 billion RuR and 18.5 million pack., which increased by 0.9% and decreased by 8.9% relative to 2019 in monetary and natural units, respectively. The fraction of local products increased yearly and was >57.1% by 2020 in monetary and 77.3% in natural sales (Fig. 8).

The average yearly sales growth for 2016 – 2020 was 5.3% in monetary and 5.8% in natural units. Sales of meloxicam in the first quarter of 2021 increased by 9.7% relative to the analogous period of 2020 with an overall drop of sales for the drugs in the set for the period.

In 2020, 62.9% of revenue (3.5 billion RuR) and 46.2% of natural sales (8.5 million pack.) came from injectable DFs (Fig. 9).

The main demand segment was the commercial sector. The state sector had practically no demand (Fig. 10). Almost all sales came from meloxicam prescription drugs.

The sales distribution of manufacturers (owners of drug registration certificates) of INN meloxicam showed an

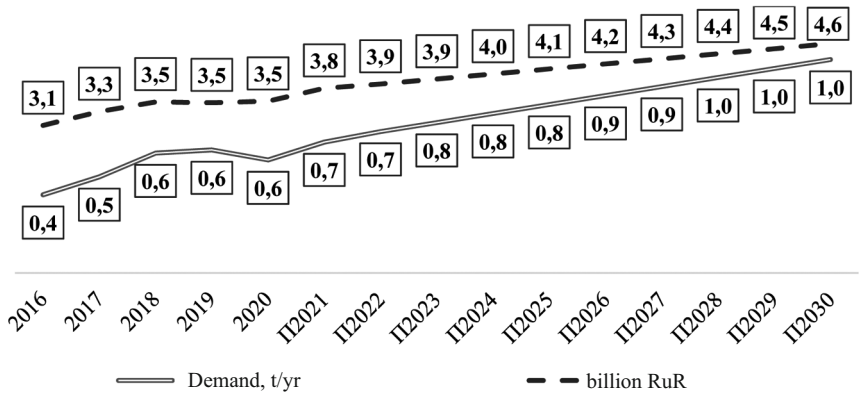

Fig. 13. Predicted monetary and natural demand for INN meloxicam in injection DFs until 2030.

oligopolistic market structure with a clear leader. The top five manufacturers held 79% of the market. Sales of the leader, the product line of which included injectables, produced 37% of total revenue for 2020.

The top five monetary sales of meloxicam by SKU were 42.7% of the market, among which were four injectables and one gel (Fig. 11).

The greatest sales volumes of meloxicam drugs in monetary units came from the Central and Volga Federal Districts with 1.6 and 1.2 billion RuR, respectively (Fig. 12).

Thus, INN meloxicam satisfied the main selection criteria for creating a microneedle DF:

1) High sales volume of injectables (greatest of the whole set);

2) High fraction of the retail sector demand;

3) ATC group M01 Anti-inflammatory and antirheumatic drugs.

Prediction of sales volumes upon market entry of a novel microneedle DF

The potential market volume from direct substitution of INN meloxicam injectables by microneedles is 3.5 billion RuR in 2020. An estimate of the market potential of INN meloxicam presupposed prediction of the demand until 2030. The demand for meloxicam drugs was converted to units of active ingredient to obtain an objective estimate of the volumes. The market volume of INN meloxicam in 2020 as injectables was 0.4 t.

The demand was predicted based on time series models, i.e., a seasonal trend model, an autoregressive integrated moving average (ARIMA) model, and a seasonal ARIMA (SARIMA). Quarterly drug sales data for 21 periods were used to make the prediction.

The ARIMA model described the sales with the least error. The mean absolute percentage error (MAPE) of the prediction was 6.7% for natural and 3.4% for monetary sales of INN meloxicam.

According to the prediction, the volume of INN meloxicam as injectables in 2030 was 4.6 billion RuR and 1.0 t/yr and increased by 1.1 billion RuR and 0.4 t/yr relative to the 2020 values with a yearly average revenue growth rate of 2.7% and 3.5% growth of natural demand (Fig. 13).

INN meloxicam met the main selection criteria and possessed adequate market potential to create a microneedle DF:

–Prediction of the market indicated stable sales growth dynamics and a potential market volume of 4.6 billion RuR by 2030. This volume was the main direct market for substitution;

–A study of the potential of the DF with respect to substitution of tablet and external DFs (gel) of INN meloxicam and substitution of other analgesics requires further clinical and economic comparisons of analgesic groups that are recommended to be performed after finding the material and technical balance for the theoretical development costs and refinement of end-user characteristics of the developed drug;

–Development of combined OA therapeutics (addition of chondroitin sulfate, sodium hyaluronate, other analgesics) had high market potential.

Thus, innovative development of the national pharmaceutical industry includes the ability to design an original product by implementing modern manufacturing technology and depends on successful integration of developments onto the global market.

At present, modern technologies with innovative drug delivery methods providing important clinical advantages over DFs circulating on the market are being targeted for investments.

According to the research results, the novel microneedle DF can be considered a technology platform that can improve the competitiveness of drugs circulating on the market and new APIs. The examined technology platform meets the priorities of science and technology development of the Russian Federation and helps to solve several problems connected with increasing the level of departmental technological competence in the framework of the State Program for Development of the Pharmaceutical and Medical Industry [32], namely:

–High-priority implementation of modern technological platforms for manufacturing novel DFs in all significant therapeutic and technological niches;

–Development of laboratory, pilot, manufacturing, and educational infrastructure in high-priority areas for implementing modern technological platforms;

–Elaboration of new measures for state support and performance of collaborative projects of pharmaceutical manufacturers and scientific and educational organizations for the transfer of modern technologies without analogs with respect to already implemented technological platforms.

The present work studied technological aspects of a novel microneedle DF and examined the clinical efficacy and possible application areas. It was shown that INN meloxicam in microneedle DF possessed both therapeutic and market potential.

ACKNOWLEDGMENTS

The results were obtained using equipment at the CCU Analytical Center, SPCPU, Ministry of Health of Russia, in the framework of Contract No. 075-15-2021-685 of Jul. 26, 2021 with financial support from the Ministry of Education and Science of Russia.

REFERENCES

1. A. C. Williams and B. W. Barry, *Crit. Rev. Ther. Drug Carrier Syst.*, **9**(3 – 4), 305 – 353 (1992).
2. J. Singh and S. Singh, *Curr. Probl. Dermatol.*, **22**, 179 – 183 (1995).
3. V. Srinivasan, W. I. Higuchi, S. M. Sims, et al., *J. Pharm. Sci.*, **78**, 370 – 375 (1989).
4. J. J. Escobar-Chavez, D. Bonilla-Martinez, M. A. Villegas-Gonzalez, et al., *J. Clin. Pharmacol.*, **49**, 1262 – 1283 (2009).
5. S. Henry, D. V. McAllister, M. G. Allen, et al., *J. Pharm. Sci.*, **87**, 922 – 925 (1998).
6. Cochrane Library; https: // www.cochranelibrary.com // (accessed May 20, 2021).
7. *Audit of the Retail and State Pharmaceutical Market in the RF*; https: // dsmviewer.ru / (accessed May 20, 2021).
8. H. Lev-Tov, *JAMA Dermatol.*, **153**(7), 631 – 632 (2017).
9. M. I. Haq, E. Smith, D. N. John, et al., *Biomed. Microdevices*, **11**, 35 – 47 (2009).
10. N. G. Rouphael, M. Paine, R. Mosley, et al., *Lancet*, **390**, 649 – 658 (2017).
11. P. M. Frew, M. B. Paine, N. Rouphael, et al., *Vaccine*, **38**(45), 7175 – 7181 (2020).
12. J. J. Norman, M. R. Brown, N. A. Raviele, et al., *Pediatr. Diabetes*, **14**(6), 459 – 465 (2013).
13. E. G. Kuznetsova, V. A. Rozhikova, L. A. Salomatina, et al., *Vestn. Transplantologii Iskusstv. Organov*, **18**(4), 87 – 92 (2016).
14. S. Y. Choi, H. J. Kwon, G. R. Ahn, et al., *Dermatol. Ther.*, **30**(6), e12546 (2017); doi: 10.1111 / dth.12546.
15. M. Avcil, G. Akman, J. Klokkers, et al., *J. Cosmet. Dermatol.*, **19**(2), 328 – 337 (2020).
16. J. Gupta, D. D. Denson, E. I. Felner, et al., *Clin. J. Pain*, **28**(2), 129 – 135 (2012).
17. J. Stahl, M. Wohlert, and M. Kietzmann, *BMC Pharmacol. Toxicol.*, **13**, 5 (2012).
18. Y. A. Gomaa, D. I. Morrow, M. J. Garland, et al., *Toxicol. In Vitro*, **24**, 1971 – 1978 (2010).
19. R. F. Donnelly, T. R. Singh, M. M. Tunney, et al., *Pharm. Res.*, **26**, 2513 – 2522 (2009).
20. Association of Rheumatologists of Russia, *Clinical Recommendations for Diagnosis and Treatment of Osteoarthritis* [in Russian]; https: // pharm-spb.ru / docs / lit / Revmatologia_Rekomendazii%20po%20diagnostike%20i%20lecheniyu%20osteoartroza%20(ARR,%202013).pdf (accessed May 20, 2021).
21. V. A. Nasonova, O. M. Folomeeva, V. N. Amirdzhanova, et al., *Nauchno-Prakt. Revmatol.*, **38**(2), 4 – 12 (2000).
22. V. A. Nasonova, *Ter. Arkh.*, No. 5, 56 – 64 (2001).
23. D. Pereira, B. Peleteiro, J. Araujo, et al., *Osteoarthritis Cartilage*, **19**(11), 1270 – 1285 (2011).
24. M. A. Kabalyk, *Nauchno-Prakt. Revmatol.*, **56**(4), 416 – 422 (2018).
25. K. M. Jordan, N. K. Arden, M. Doherty, et al., *Ann. Rheum. Dis.*, **62**, 1145 – 1155 (2003).
26. M. C. Hochberg, R. D. Altman, K. T. April, et al., *Arthritis Care Res. (Hoboken)*, **64**(4), 465 – 474 (2012).
27. T. E. Alindon, R. R. Bannuru, M. C. Sullivan, et al., *Osteoarthritis Cartilage*, **22**(3), 363 – 388 (2014).
28. National Clinical Guideline Centre (UK), Osteoarthritis: Care and Management in Adults, National Institute for Health and Care Excellence, London (UK); 2014 Feb. PMID: 25340227.
29. R. Wittenauer, L. Smith, and K. Aden, Background Paper 6.12 Osteoarthritis. Priority Medicines for Europe and the World "A Public Health Approach to Innovation" Update on 2004 background paper, January 28th 2013. World Health Organization; https: // www.who.int / medicines / areas / priority medicines / BP6_12Osteo.pdf (accessed May 20, 2021).
30. Global Data Report "Opportunity Analyzer: Osteoarthritis — Opportunity Analysis and Forecasts to 2026"; https: // store.globaldata.com / report / gdhc073poa-opportunityanalyzer-osteoarthritis-opportunity-analysis-and-forecasts-to-2026 / (accessed May 20, 2021).
31. Association of Rheumatologists of Russia, *Federal Clinical Recommendations for Diagnosis and Treatment of Osteoarthritis*; https: // rheumatolog.ru / sites / default / files / Pdf / clinrec / osteoartrit.docx / (accessed May 20, 2021).
32. Decree No. 305 of the Government of the Russian Federation of Apr. 15, 2014, "On approval of the state program of the Russian Federation 'Development of the pharmaceutical and medical industry'" (with amendments of Mar. 31, 2021).