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Аспекты применения индометацина в медицине и фармации

Синтезированный в шестидесятых годах прошлого столетия типичный представитель класса нестероидных противовоспалительных средств индометацин нашел широкое применение в различных областях медицины. Сочетание противовоспалительного и обезболивающего действия обусловило успешное применение индометацина при ревматических заболеваниях. Новейшие исследования выявили, что препарат может стать перспективным средством и в терапии ряда иных патологий. В статье приведен краткий обзор ассортимента современных препаратов и различных лекарственных форм индометацина на отечественном фармацевтическом рынке. Одним из факторов, снижающих биофармацевтические характеристики препаратов индометацина, является его малая растворимость в воде. Согласно результатам анализа литературных данных, одной из перспективных технологий, способных успешно увеличить растворимость и биодоступность индометацина, является метод получения его твердых дисперсий. Твердые дисперсии — это би- или многокомпонентные системы из лекарственного вещества и носителя, представляющие собой высокодиспергированную твердую фазу лекарственного вещества или молекулярно-дисперсные твердые или жидкие растворы с частичным образованием комплексов переменного состава с материалом носителя. Представлен краткий обзор работ, посвященных различным аспектам получения, исследования и применения твердых дисперсий индометацина с разными полимерами-носителями.

***Ключевые слова**: индометацин, твердые дисперсии, полимеры, растворимость, биодоступность.*
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Introduction

Indomethacin is one of the most widely used NSAIDs in modern medicine. T.Y. Shen et al. synthesized indomethacin at Merck, Sharp and Dome laboratory, New York. The medication's chemical properties and production method were first described in 1963. A lot of clinical trials were conducted thereafter which highlighted advantages of indomethacin over pyrazolone derivatives (amidopyrine and phenylbutazone) and salicylates (Aspirin) [1]. Combined administration of indomethacin and steroid drugs was proved to enhance the effect of the latter. Due to anti-inflammatory and pain relieving effects, indomethacin was successfully used in rheumatoid diseases such as rheumatoid arthritis, osteoarthritis, arthritic gout, and ankylosing spondylitis. Indomethacin was the first nonsteroidal drug which ensured consistent reduction of joint swelling in rheumatoid arthritis. Moreover, it became the drug of choice in arthritic gout. Commonly reported side effects of indomethacin include headache, dizziness, asthenia, and dyspepsia. Due to therapeutic benefits indomethacin has become the gold standard of NSAIDs.

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Application of Indomethacin in Medicine and Pharmacy

Indomethacin, a non-steroid anti-inflammatory drug (NSAID), has been used in different spheres of medicine since the 1960s. It is successfully administered as an anti-inflammatory and pain-relieving medication in rheumatoid and other diseases. According to recent research, indomethacin may become a promising drug enhancing endogenous remyelination in patients with multiple sclerosis. Also, indomethacin affects cell proliferation and invasion, thus it is used to manage pancreatic cancer in patients with hyperglycemia. In addition, indomethacin can inhibit protein synthesis in colorectal carcinoma and other types of cancer cells. The article reviews modern indomethacin medications and the different dosage forms on the Russian pharmaceutical market. Indomethacin poor water solubility is one of the reasons for decreasing its biopharmaceutical characteristics. According to the conducted research, a prospective way to improve indomethacin solubility and bioavailability is the Solid Dispersion (SD) method. SDs are bi- or multicomponent systems consisting of the drug and the carrier. They are a highly dispersed solid phase of the drug or molecular-dispersed solid solutions with a partial formation of a variable composition complex and a carrier. The article provides a brief overview on different aspects of obtaining, investigating, and applying indomethacin SDs with various polymers.

***Key words**: indomethacin, solid dispersion (SD), polymers, solubility, bioavailability.*
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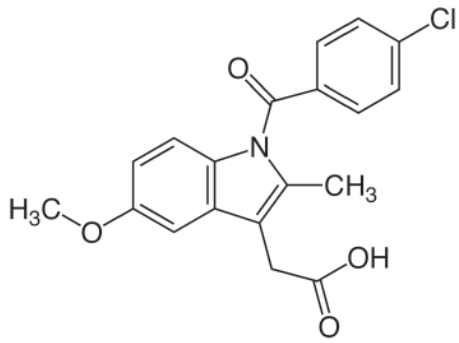

Fig. Indomethacin. Molecular weight 357.793 g/mol

Indomethacin is a synthetic nonsteroidal indole derivative 2-[1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetic acid (Fig.).

According to drug physical properties, indomethacin is white to pale-yellow odorless crystalline powder [2, 3]. Crystals exhibit polymorphism with one form of polymorphic crystals melting at about 155 °C and the other at about 162 °C, respectively [3]. Indomethacin is soluble in ether, acetone and castor oil; sparingly soluble in ethanol, practically insoluble in water (0.937 mg/L at 25 °C) which limits its application in pharmaceutical technology and decreases some parameters of its dosage forms. The medication is stable in neutral or slightly acidic media and is decomposed by strong alkali [2]; stored at temperature below 25 °C away from light and moisture [2, 3].

Indomethacin is one of the most active NSAIDs [4]. Its pharmacological activity includes nonselective inhibition of the enzyme cyclooxygenase (COX) and partial blocking of prostaglandin biosynthesis thus providing anti-inflammatory, analgesic, and antipyretic effects. The inhibition of COX-1 leads to suppression of thromboxane A2 synthesis which results in reversible reduction of platelet aggregation [3].

Indomethacin dosage forms are widely used in different areas of medicine. The drug is systemically administered in inflammatory and degenerative musculoskeletal diseases (articular syndrome, spine pain, traumatic inflammation of soft tissues and joints, rheumatism), pain syndrome (head and toothache, myalgia, neuralgia, pain after trauma and surgery accompanied with inflammation). In cases when potential benefits outweigh side effects, the drug is prescribed in algodismenorrhea, inflammatory processes in the small pelvis, pericarditis, and in premature birth. It is used as an adjuvant in ENT disorders with acute pain syndrome. Also, it is applied topically in ligament, tendon, muscle and joint inflammation after traumas. In ophthalmology indomethacin is prescribed to inhibit myosis in cataract surgery, inflammation after surgery, and noninfectious conjunctivitis. In dentistry it is administered in arthritis and arthrosis of the temporomandibular joint and oral tissues inflammatory disorders [3].

According to recent research, indomethacin may become a promising drug improving endogenous remyelination in patients with multiple sclerosis. It can cross the blood-brain barrier and stimulate oligodendrocytes formation from their progenitor cells [5]. Via up-regulating E-cadherin, coded by CDH1 gene suppressor [6], indomethacin affects cell proliferation and invasion, thus it is used to manage pancreatic cancer in patients with hyperglycemia [7].

Due to its ability to selectively activate the double-stranded RNA-dependent protein kinase and cause rapid phosphorylation of eIF2α, Indomethacin can inhibit protein synthesis in colorectal carcinoma and other types of cancer cells, which makes it a promising drug in cancer management [8].

Indomethacin Preparations

Ten brand names of indomethacin are currently available on the Russian pharmaceutical market. They are as follows: Indomethacin, Indobene, Indocollyre, Indomethacin 100 Berlin-Chemie, Indomethacin 50 Berlin-Chemie, Indomethacin Sopharma, Indomethacin-Akri, Indomethacin-Altpharm, Indomethacin-Biosintez, and Metindol Retard. Most Indomethacin dosage forms are manufactured by the following Russian companies: JSC Murom Apparatus Producing Plant, OJSC Biosintez, OOO (a limited liability company under the laws of Russian Federation) Ozon, JSC Pharmaceutical Factory Obolenskoe, Akrikhin, and OOO Altpharm. Foreign Indomethacin preparations are produced in Germany (Merkle GmbH., Berlin-Chemie AG), France (Laboratoire Chauvin SA), Poland (ICN Polfa RzeszÓw SA), Bulgaria (Sopharma AD, Balkanpharma Dupnica AD, Balkanpharma Troyan AD, VetProm AD), Belarus (Borisovskiy Zavod Medicinskikh Preparatov OJSC), Moldova (Farmaprim).

Pharmaceutical substances to produce indomethacin preparations are manufactured in China (Taicang Pharmaceutical Company, CSPC Pharmaceutical Group Limited, Shijiazhuang GroupZhongnuo Pharma Co., Ltd.).

Indomethacin is administered orally, intramuscularly, rectally, and locally. The initial adult dose prescribed orally after meals is 25 mg 2–3 times a day. Then a daily dose is increased to 100–150 mg (3–4 times a day) depending on the drug tolerance. 75 mg (1 capsule) of indomethacin retard is taken once or twice daily (in the morning and in the evening) 5–10 days, then 1 capsule a day in the evening [4].

The brand name of coated tablets manufactured by the Russian company OJSC Biosintez is Indomethacin-Biosintez. Enteric coated tablets are Indomethacin (Russia, Bulgaria) and Indomethacin Sopharma (Bulgaria). Prolonged release tablets are Metindol Retard (Poland) [2]. Effervescent tablets containing indomethacin, caffeine and prochlorperazine to treat headache are manufactured by E-Pharma Trento S.P.A. (Italy) but they are not registered in Russia. Rectal suppositories of 50 mg or 100 mg are administered twice daily [4]. They are Indomethacin-Altpharm by OOO Altpharm and indomethacin manufactured by Farmaprim and OJSC Biosintez. Also, foreign companies produce rectal suppositories under the following brand names: Indomethacin (Croatia and Moldova), Indomethacin 100 Berlin-Chemie, Indomethacin 50 Berlin-Chemie (Germany), Indomethacin Sopharma (Bulgaria) [2]. To treat acute conditions, indomethacin is administered intramuscularly — 60 mg once or twice daily for 7–14 days followed by tablets or suppositories. Indomethacin ointment is applied topically in acute and chronic polyarthritis, neuritis, plexitis, radiculitis, thrombophlebitis and arthropathic psoriasis. The total daily amount should not exceed a 15 cm length of ointment squeezed from the tube for adults and 7.5 cm for children [4]. Indomethacin 10% ointment is produced by national factories JSC Murom Apparatus Producing Plant, OJSC Biosintez, OOO Ozon and foreign companies (Belarus, Bulgaria). Indomethacin-Akri, Indomethacin-Biosintez, and Indomethacin Sopharma 10% ointment are manufactured by the Russian companies Akrikhin, OJSC Biosintez, and Bulgarian Sopharma AD, respectively.

Indomethacin gel is represented by a German medication Indobene (1%) and by a Bulgarian preparation Indomethacin (5% and 10%) [2]. Eftimethacyn, the ointment produced by the Russian company Medic LDF and containing aminophylline, diphenhydramine, and indomethacin, is used to treat diseases of the musculoskeletal system. Gel containing indomethacin and angioprotector troxerutin is manufactured in Bulgaria by VetProm AD, Balkanpharma Troyan AD under

the brand names Troximethacin and Indovasin, respectively. These medications are used in combination therapy in chronic venous insufficiency of lower limbs, superficial thrombophlebitis, rheumatoid lesions of soft tissues, and postsurgical edemas. In ophthalmology indomethacin drops are administered in noninfectious inflammatory processes, e.g. after surgery [4]. Ophthalmological medications include eye drops Indocollyre produced in France.

Despite its wide application and high efficacy, indomethacin has pronounced side effects which is critical to widespread administration. The main mechanism of NSAIDs side effects lies in the main therapeutic mechanism. The medications inhibit the synthesis of protective specific prostaglandins in the mucous layer of the gastrointestinal tract (GIT) which leads to peptic ulcerative lesions of the stomach and the duodenum. According to endoscopic studies, such adverse events occur in 10–20% of patients administered NSAIDs on a regular basis. Along with the risk of arterial hypertension, bronchospasms, toxic hepatitis, thrombopenia, cardiac rhythm disorders, indomethacin negatively affects the GIT [2, 4] which is typical for patients receiving the most commonly prescribed oral dosage form. Side effects include nausea, vomiting, pain in the epigastrium, erosive ulcerative lesions of the GIT, gastrointestinal and rectal bleeding. Thus, indomethacin has a wide range of contraindications, including erosive ulcerative lesions of the GIT and some forms of enterocolitis [9]. To prevent and decrease dyspeptic disorders, indomethacin should be taken with milk during or after meals along with antacids. The medication is contraindicated in bronchial asthma, thrombopenia, and renal insufficiency; should not be administered in pregnant women because of its teratogenic action [4]. Another drug disadvantage is its low water solubility which decreases its BA. It requires high-dose intake which increases the risk of side effects [9]. Similar to other anti-inflammatory drugs, indomethacin is a drug of long term administration and its anticipatory discontinuation may lead to disease recurrence which highlights the necessity for dose decrease in terms of safe intake.

There are different dosage forms of indomethacin. They are tablets of 5, 10, and 25 mg (N. 10, 30, 50); prolonged release tablets of 75 mg (N. 25, 50); pills of 25 mg (N. 30); capsules of 25, 30, and 50 mg (N. 20, 30, 50); capsules retard of 75 mg (N. 10, 50); rectal suppositories of 50 and 100 mg (N. 5, 10); 3% injection solution in 2 ml ampules; 1% and 10% gel in 50 and 100 gr tubes; 5% and 10% ointment in 30 and 40 gr tubes; 0.1% and 1% eye suspension; 0.1% eye drops. Shelf life of indomethacin-containing drugs varies according to the manufacturer and dosage form: tablets can be stored from 3 to 5 years, capsules — 4.5 years, ointment and gel — from 2 to 3 years, suppositories — 3 years, eye suspension — 2 years [4], eye drops — 1.5 years. Rectal suppositories, 10% ointment, enteric coated tablets and coated tablets are produced in Russia, while gel, eye drops and prolonged release tablets are manufactured by foreign companies only. Pills, capsules, injection solution and eye suspension of indomethacin are not presented on the Russian market as state license is expired.

Indomethacin dosage forms with improved solubility

The issue of drug solubility improvment is one of interest for the current research which stresses the importance and timeliness of improving and designing Indomethacin-containing drugs. Many studies focused on the ways for reducing indomethacin side effects. Different micro- and nanocarriers based on biodegradable polymers have been developed. Microencapsulation of indomethacin into biodegradable particles of polylactide-glycolide and its copolymer polylactide-polyethelene glycole using compressed CO_2 allowed getting sustained release of the model drug [10]. Desired compositions of indomethacin sustained release microcapsules using ethyl cellulose, hydroxy propyl methyl cellulose, and chitosan-carboxymethyl-cellulose are described [11].

A pharmaceutical composition of indomethacin encapsulated in phospholipid nanoparticles with increased antirheumatoid and anti-inflammatory activity when taken orally and intravenously was designed and patented by Russian scientists in 2011. When administered to rats orally, indomethacin BA increased two-fold compared to the drug in its free form [9, 12]. A pharmaceutical composition of indomethacin encapsulated in phospholipid nanoparticles patented in 2012 is one of the up-to-date developments in ophthalmology [13].

Another study concerning the production of poly (vinyl acetate) nanoparticles with indomethacin incorporated in them to include in ophthalmic formulations describes a sustained release dosage form [14]. A group of scientists from China synthesized mesoporous silica nanospheres functionalized with aminopropyl groups which include the drug coated with a natural organic polymer alginate (ALG). Sustained release of indomethacin was mainly due to the blockage effect of the coated ALG [15]. Ways to form indomethacin microspheres using natural and synthetic polymers (albumin, ethyl cellulose and Eudragit L100) are described [16].

One more study focused on the emulgel system of indomethacin using 2 types of gelling agents: Carbopol 934 and Xanthan Gum which has higher drug release and desired physical properties (color, homogeneity, consistency, spreadability, pH value) [17].

To solve the problem of indomethacin poor solubility, a promising approach to advance the technology of drug formation and increase BA — SD method — was used. SDs are bi- or multicomponent systems consisting of the drug and the carrier. They are a highly dispersed solid phase of the drug or molecular-dispersed solid solutions with a partial formation of a variable composition complex and a carrier [18, 19]. Russian and foreign studies on Indomethacin solubility improvement with polymers such as hydroxy propyl methyl cellulose, Soluplus, polyvinyl acetate, polyethelene glycol (PEG), and polyvinylpyrrolidone (PVP) of different molecular weights were used to produce SD [9, 20].

Another study analyzed the drug permeability across Caco-2 monolayers and revealed that the drug absorption increased four-fold when reformulated as SD with hydrophilic PEG 8000 compared to the drug in its free form. It may be explained by transition of the drug from the crystalline to amorphous state upon dispersing within PEG matrix. The study demonstrated no chemical interaction between the drug and the carrier [20]. The research stated that SD method greatly influences the stability of the drug amorphous state and the drug concentration in the solution. The polymers added as pre-dissolved solutions generated higher supersaturation concentrations of the drug. In contrast, SDs maintained supersaturation for longer [21].

Prospects of Indomethacin Solid Dispersion

Many years have passed and a lot of research has been done since indomethacin was synthesized and introduced in clinical practice. Thus, all pharmacological and technological aspects of its implementation have been thoroughly studied. The chemical substance indomethacin is an active

agent widely used in various dosage forms: tablets, prolonged release, capsules retard, rectal suppositories, ointment, and eye drops.

The substance may seem to have lost its innovative potential. However, this opinion is inaccurate. Scientists of the I.M. Sechenov First Moscow State Medical University have been conducting research to enhance bioavailability of poorly water soluble drugs by means of the solid dispersion method, using polymer carriers for many years. This approach has been used to investigate over 30 poorly water soluble substances from different pharmacological groups for the last 15 years [18, 22–25].

The solid dispersion method allows improving biopharmaceutical characteristics of substances including solubility improvment. Therefore, it enables us to widen the scope of the newly synthesized and well-known substances application enhancing bioavailability and reducing side effects.

Modern research in Russia aims at developing innovative dosage forms with advanced pharmaceutical characteristics, containing indomethacin solid dispersion which may become competitive among national and foreign pharmaceuticals.

Conclusions

Indomethacin is one of the most active NSAIDs used as an antipyretic, pain relieving, and analgesic medication. There is a wide range of dosage forms both national and foreign on the pharmaceutical market in the Russian Federation. However, the substance is poorly water soluble and has a number of side effects. SD method to increase indomethacin solubility and dosage forms design is a pressing issue in modern pharmacy. Therefore, the Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University of the Healthcare Ministry of the Russian Federation conducts detailed research to produce indomethacin SDs with polymers to enhance its solubility which enables to further develop highly soluble dosage forms with enhanced BA and reduced side effects.

Authors conflict of interests statement

Authors claim that there is no conflict of interest associated with this work.

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