Pharmacokinetics of Piroxicam Pharmaceutical Forms: an Experimental Study

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Abstract

Research into new ways to administer medications within the body remains relevant. The study aims to analyze the particularities of piroxicam kinetics in zein-pectin complexes during ex vivo experiments in a medium simulating the gastrointestinal tract of laboratory rats. Studies were performed in 2019 with 30 laboratory Wistar rats. During 3 days, rats received 2.5 ml of 2% pectin solution per day. The ratio between pectin and zein was 3:1. Rats were mortified, and their intestines were then dissected into 3-cm fragments. The obtained samples were placed in containers with 5 ml of saline phosphate buffer solution (solution pH = 6.4). Gastrointestinal contents and pectin apple and citrus complexes with low methylation were incubated to study the kinetics of piroxicam. Pectin complexes varied in dry carrier mass: the citrus complex was 1.3 times greater than the apple complex (pd"0.05). It was also observed that the release time of 50% of the volume of piroxicam was 1.3 times faster for the citrus complex (pd"0.05) than for the apple complex. In terms of swelling index, citrus complexes were 1.9 times larger than apple complexes (pd"0.01). Citrus complexes contained a lower concentration of piroxicam (1.3 times, pd"0.05) relative to apple complexes. The long-term effect of piroxicam release from pectin complexes was established during the experiment. This is likely due to the slow swelling of the ion part of the polymer mesh under hydrophobic solution conditions. The latter was represented in the experiment by the phosphate buffer and the content of the gastrointestinal tract. The limiting factor that influenced the release kinetics of piroxicam from pectin complexes is its diffusion process from the pectin complex. A high correlation was observed between the 50% piroxicam release and the square root of time in both complexes (0.98). Apple pectin was 3.0 times larger than the constant (p d"0.01). The kinetics analysis demonstrated their linear directionality over approximately 40 hours.

Keywords: Pyroxicam, kinetics, experiment, low-methylated apple pectin, low-methylated citrus pectin, complexes, drug delivery methods.

Introduction

Many people, in particular the elderly, suffer from joint and spinal pain caused by rheumatoid arthritis, spondyloarthritis, and osteoarthritis. According to the World Health Organization, the pain accompanying these musculoskeletal disorders affects a large proportion of the population, from 20% to 45%(1). There is not only age but also gender dependency, i.e., women suffer more than men. Pain syndrome is caused by inflammation of the synovial membrane of the joint and is considered a chronic disease. The severity of the pain syndrome is not always a reflection of the inflammatory process (2). Inflammation is typically caused by several factors, including increased levels of pro-inflammatory agents, as well as the proliferation of immune cells, and increased activity of the metalloprotease enzymes(3).

Treatment of rheumatoid arthritis and spondyloarthritisis prolonged, with patients continually taking anti-inflammatory drugs and painkillers.This therapy may last for years since there are virtually no confirmed cases of remission(4).In this regard, a necessary and mandatory requirement for medicines is the presence of a fast effect, the force of expression, as well as the easy tolerability of the body after intake(5). Risk factors include the advanced age of most patients, along with the presence of comorbidities.For instance, among the 9,000 patients interviewed in Serbia, 60% had comorbidities (6). Comorbid diseases in osteoarthritis are most often obesity, diabetes, arterial hypertension,and coronary heartdisease. That was shown in acomparison of more than 11,000 patientswithosteoarthritis and the same number of patientswith out it in the UK (7). Patients with osteoarthritis were 1.6 to 2.2 times more likely to experience gastritis, obesity, coronary artery disease, esophageal hernia, and phlebitis.

Continued use of anti-inflammatory drugs increases the risk of congestive heart failure. When this disease is present, anti-inflammatory drugs may heighten the risk of increasing failure for 10 times. In people with no corresponding diagnosis, the risk of congestive heart failure and subsequent hospitalization is 2.0 times greater (8,9). This suggests that the major current requirements for anti-inflammatory drugs are efficacy and analgesic effect, as well as safety (10).

Piroxicam refers to anti-inflammatory agents with anti-aggregating, analgesic, and antipyretic effects(11). Piroxicam is used to treat various conditions of the musculoskeletal system, whereas also against neuralgia, myalgia, post-traumatic pain, gout, soft tissue inflammation, and inflammatory infectious diseases of the upper respiratory tract(12). The mechanism of piroxicamaction is to block the COX-1 and COX-2 systems in the metabolization of arachidonic acid.A characteristic feature of piroxicam is high absorption when taken orally, along with the

duration of the effect of up to 1 day after the first dose.Therefore, piroxicam may be taken 1-2 times daily, depending on the dosage form(13).

Based on piroxicam, novel medicines are developed in modern pharmacology.Furthermore, the mechanisms of action are studied according to the age group(14-16).Piroxicam is a widely used and highly sought-after anti-inflammatory medication.To a great extent, the tolerance, pharmacokinetics and ease of use of the medication for the patient depend on parameters such as pharmaceutical dosage form.Ease of use and tolerance also largely determine the commitment of the patient to treatment.The success of the treatment, in turn, is dependent on compliance.The presence of low-soluble or insoluble compounds in the liquid dosage form plays a major role since they can facilitate oral administration and thereby increase patient comfort(17).

Piroxicam is available in various dosage forms, such as tablets, suppositories, capsules, and gels (external use). Within the CIS countries, seven manufacturers are registered, originating in four countries – Germany, Poland, Bulgaria, and the Russian Federation. It should be noted that all oral forms offered by these manufacturers have a similar composition of excipients, which determines the little choice between them.

Recently, among oral dosage forms for prescription by doctors, preference is given to fluid forms(18). In this regard, there is an urgent problem with the current development of a fluid dosage form of piroxicam. Such a development would increase the choice between various variants of piroxicam drugs, taking into account excipients, patient preferences, and pharmaceutical parameters.

Piroxicam is notoriously insoluble in water and is thus also used as a suspension (19). Suspension is characterized by several features that give it benefits over other dosage forms. These include high dispersibility of the solid fraction, faster onset of therapeutic effect compared to

tablets and other solid dosage forms, prolonged therapeutic effect compared to solutions, and ease of use by patients. Piroxicam suspensions represent no more than 1.5% of the total quantity of the medication in various dosage forms. These small figures can be explained by the fact that, as a general rule, suspensions are unstable in a kinetic and aggressive manner, which determines the particularities of the storage and preparation of suspensions.

Consequently, the effective dosage forms of piroxicam available are unstable under storage conditions, which has determined the relevance of research into other drug delivery systems in the human body. The study aims to examine peculiarities of piroxicam kinetics in ex vivo experiments in the gastrointestinal tract. The authors suggest that using a potentially suitable material, i.e., pectin and zein-based hydrogels, could provide an alternative as a more efficient way to deliver piroxicam to the gastrointestinal tract lumen during oral administration. The objectives of the study were: (a) to analyze the kinetics of piroxicam releases from hydrogel-based drug delivery systems under gastrointestinal conditions during an experiment on rats; b) to compare the experimental results obtained depending on the ratio of zein and pectin, dry matter mass and mass index of piroxicam; c) to estimate the time interval for which 50% of piroxicam is released under conditions simulating the gastrointestinal tract.

Materials and Methods

The study was performed in 2019 inZakusov Institute of Pharmacology (Moscow, the Russian Federation).Two types of pectinswere applied to formhydrogel drug delivery systems: a) pectin isolated from citrus fruits; b) pectin isolated from apples. Bothtypes were low-methylated. Zein, derived from skimmed corn flour, was used as well.Pectin complexes ranged in weight from 50 to 100 mg. Additional information on piroxicam doses and zein-pectin ratio can be found in Table 1.

A population of 50 Wistar ratsfed on a standard dietary ration was used as subjects in the experiment. The average weight of the animals was 223.5 ± 10.5 g, varying between 200 to 250g.

Study design : The animals were given 2.5 ml of 2% pectin solution for three days. The injection was performed with a Teflon tube, the procedure was performed once a day. Pectin injection is required for pectolytic enzymes to appear in the lumen of the gastrointestinal tract during this period. The experimental procedure was prepared following the instructions on working with an animal, ethically, following the recommendations of the U.S. Department of State Agriculture Laboratory (20) and International Guidelines for Biomedical Research Using Animals (21). Three days after injecting 10 ml of pectin solution into 1 kg of body weight, all rats were mortified. The kill was made by carbon dioxide (CO_2) in a separate room. For this purpose, the gas was supplied through a nozzle slowly, as deviant behavioral reactions of the animals might occur when the concentration of CO_2 changes drastically. The gas was administered at 25% of the cage volume, where 20% of the volume was equivalent to 1 L of gas per minute.

After the animals died, the abdominal chamber was opened.By dissection, the intestinal tract was extracted outwards.The intestine was cut into fragments 3-4 cm long; 3 sections were circumcised in the small intestine and the same number – in the large intestine.Samples obtained were then placed in containers with 5 ml of phosphate buffer saline solution (pH of the solution = 6.4).

Experimental part: To study the kinetic process of the drug (piroxicam), GI contents and pectin complexes were incubated.To this end, pectin complexes that undergone swelling were placed in dialysis bagstogetherwith intestinal contents and phosphate buffer.The resulting solution was placed in a dissolution rate measuring device (DT 600 HH Dissolution Tester LB-550, ERWEKA, Germany).This unit was connected in line with

another, a UA-5 ISCO UV spectrophotometer, USA, which was filled with a 0.4 L phosphate buffer solution at a temperature of 37 !.The extinction of solutions was measured at the value of 337 nm. By verifying the standard piroxicam release chart, the quantitative indices of the drug released were revealed.

Calculations

The quantitation of released piroxicam was calculated using the Higushi equation (1):

$$\backslash Q = kt^{1/2} \text{(Equation 1)}$$

Where Q is the amount of pyroxicam released by pectin compounds, k is a constant, and t is time.Pyroxicam kinetic data were processed using the Pepass equation (2):

$$Mt/Mo = Ktn \text{ (Equation 2)}$$

In which Mt/Mo denotes the quantities of piroxicam released, the designations k, t correspond to those in Equation 1, and n is the rate of piroxicam release from pectin complexes.

Statistical indices were calculated using Statistica v. 6.0 (StatSoft Inc., USA). Pearson correlations were calculated under the normal distribution. Significant differences between the parameters (swelling, dosage, and time of 50% piroxicam release from pectin complexes) were established by applying a two-sample t-test for independent samples. The differences were significant at p d" 0.05.

Results

It was established that the same ratio of zein and pect in of differentorigin(appleandcitrus) exhibited differentvalues of swelling,dosage,and release rate of 50% piroxicam from pectin complexes (Tables 1, 2).

Thus, the complexes differed in a mass of dry matter (carrier) in favor of the citrus pectin complex by a factor of 1.3 (pd"0.05, Table 1). Consequently, the citrus complex may carry a greater amount of dry material. The dose of piroxicam in both complexes did not differ, whereas the release time of 50% of piroxicam in apple and citrus complexes varied significantly.

Thus, 50% of piroxicam was released 1.3 times faster by the slightly methylated citric complex (p d" 0.05) compared to the apple complex (Table 1).

There were also notable differences in swelling indices (Table 2). Low-methylated citrus complexes were 1.9 times larger than apple complexes (p d" 0.01). Furthermore, citrus complexes had slightly lower levels of piroxicam (1.3 times, pd" 0.05) than apple complexes. Finally, a strong correlation was observed between the 50% piroxicam release values and the square root of time for both types of complexes (Table 2). Meanwhile, apple pectin showed a value 3.0 times higher than the constant (pd" 0.01).

The comparison of kinetic curves showed their linearity over forty hours (Fig. 1 and 2). The low-methylated citrus pectin is characterized by a strong release of piroxicam at the initial stage of the experiment, with an additional transition towards a linear relationship (Fig. 1). For apple pectin, piroxicam production is slightly slower, reaching 40% in just two days.

The rapid release of piroxicam occurs under experimental conditions in about 45 hours when apple and citrus pectin are broken down by digestion. The transfer of piroxicam before the rupture of pectin occurs through the polymer mesh during swelling of pectin. Following the rupture of the mesh, there is a sudden release of piroxicam in the external environment (in this case, intestinal lumen).

When comparing the Higuchi curves for piroxicam released in citrus and apple complexes according to the square root of time, a clear linear relationship is established (Fig. 2). When comparing apple and citrus pectins, the release rate of piroxicam from citrus complexes was found to be more rapid. The constant of 0.20 (Table 2) for the citrus complex indicates compliance with Fick's law of diffusion, while for the apple complex, this figure corresponds to abnormal processes in drug release.

Table 1: Quantitativeandqualitativecharacteristicsofpiroxicamreleaseinexvivoexperiment depending on dosage, release time, and amount of drymatter.

Drug administration method	Ratio of drug delivery components	Weight of dry matter, mg	Dosage of pyroxicam in complexes, mcg	Release time of 50% pectin piroxicam from pectin complexes, h
Zein + low-methylatedapple pectin	1 : 3	6.29	1000	48
Zein + low-methylatedcitrus pectin	1 : 3	8.35	1000	36

Table 2 : Physical and chemical features of pectin compounds in the experiment.

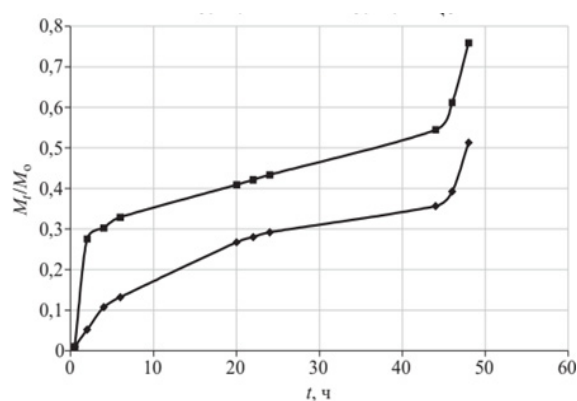| Drug a dministration method	Concentration of piroxicam in complexes, mg per 1 g	Swelling indices	Dependence of pyroxicam release rates from complexes on the square root of time	Correlation Indicators of n	The value
Zein + low-methylatedapple pectin	159.0	7.19	6.03	0.979	0.60
Zein + low-methylatedcitrus pectin	118.0	13.66	4.95	0.986	0.20

Fig. 1 Characteristics of pyroxicam release from pectin complexes in the experiment: upper line – low-methylated citrus pectin; lower line – low-methylated apple pectin.
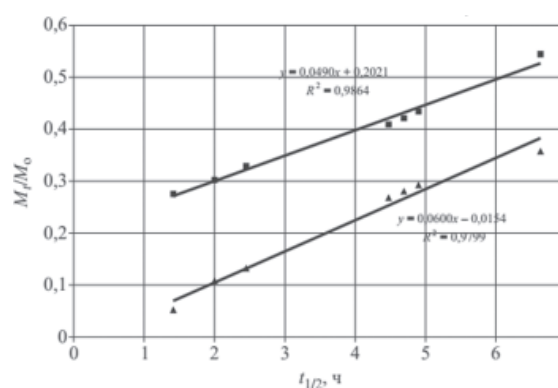

Fig. 2 Higuchi curves showing the correlation between the quantities of piroxicam released in low-methylated citrus (top row) and apple (bottom row) complexes and the square root of time.

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Discussion

When developing a new method of drug administration, the diffusion index plays a major role in revealing the concentration of the drug released(22).Inthediffusionofdrugsincapsules, many factors are significant.Particularly notable is the structure of the polymer mesh, the swelling time of the polymer and its composition, as well as the quantitative indicators of water in the solution and associatedsubstances(23).The reduction in release rates of the drug substance may be due to a combination of these factors following the implementation of physical or chemical processes.

The data provided allowed establishing a fairly widespread temporal effect of the piroxicam release from pectin complexes under experimental conditions. It can be explained by the slow effect of swelling on the ionic side of the polymer mesh under conditions of the hydrophobic solution, which is represented by phosphate buffer and the contents of the gastrointestinal tract. The limiting factor that influences the rate of piroxicam release from the pectin complexes is the process of its diffusion from the polymer component. The triple difference in the value of constants for apple and citrus pectin indicates the ability of the polymer structure of these complexes to respond clearly to external stimuli. It follows that the type of drug administration method proposed by the authors and tested in the experiment meets the requirements of pharmacology due to the ease of drug delivery to the lumen of the gastrointestinal tract. Furthermore, these biopolymers can be broken down by enzymes, which means that they are adapted to the oral administration of drugs with limited bioavailability.For patients, the potential for accurate dosing and administration of the drug substance in pectin complexes is ensured.

As far as the kinetics of piroxicam are concerned, the main number of studies is devoted to comparing it with other more modern analogues (24,25). For example, the disadvantages of intramuscular piroxicam in rabbits versus meloxicam have been demonstrated. Piroxicam caused necrosis in the injection site, as did diclofenac (26). Another study involving 599 patients found that one week after parenteral administration, shoulder pain also decreased in the group of patients taking piroxicam and the group taking meloxicam.At the same time, piroxicam had a smaller pain-relieving effect compared to meloxicam. For meloxicam at a dosage of 7.5 - 15.0 mg, pain in most patients decreased as early as day 3 of administration, whereas in the group taking piroxicam, pain reduction was noted after 7-10 days at a dosage of 20 mg (27). Piroxicam is primarily prescribed for youth who do not have comorbidity and is not prescribed for older patients who may have disease complications caused by piroxicam intake(28,29). Despite this, piroxicam was used as a model drug in this work, and its kinetic properties determine the diffusion rate according to the method of drug administration.

Conclusions

It was noted that the primary role in the piroxicam release from pectin complexes is played by diffusion indices. Pectin complexes of different origins (apple and citrus) are filled with the drug differently, demonstrating different degrees of swelling. This defines the differences in the release kinetics of piroxicam as it enters the gastrointestinal tract. Thus, with the apple complex, there is a slower piroxicam release with only 40% of the medication volume expressed for 2 days. On the other hand, the degradation of the biopolymer results in a high release of piroxicam. The citrus complex is characterized by a faster piroxicam release rate at the initial stage of entering the gastrointestinal tract environment with further linear dependence. The proposed method of drug administration provides efficient, quick, and safe delivery of the medication at the right concentration to the lumen of the GI tract. At the same time, further testing of pectin complexes on other medications is required.

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Competing interests. The authors declare that they have no competing interests.

Availability of data and materials. Data will be available on request.

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