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FROM PHARMACEUTICAL PROPERTIES OF BISMUTH DRUGS TO CLINICAL EFFICACY

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Abstract. The article considers the pharmacodynamics, pharmacokinetics and clinical aspects of the use of bismuth tripalium dicitrate, and also conducts a comparative analysis of the physicochemical and structural properties of tablet forms of drugs containing bismuth tripalium dicitrate - the original drug De-Nol (Astellas) and a generic, a new product Ulcavís (KRKA). The demonstrated similar physicochemical properties, in particular the same rate of disintegration of the two tablet forms of bismuth tripalium dicitrate, suggest similar clinical efficacy of the generic and the reference drug.

Keywords: colloidal bismuth, H. pylori, functional dyspepsia, bismuth tripotassium dicitrate, pharmaceutical equivalence.

INTRODUCTION

Bismuth preparations (bismuth tripotassium dicitrate, subsalicylate, subnitrate, subcarbonate) have been used in medicine since the 17th century to treat various diseases of the gastrointestinal tract (GIT). Currently, there is a kind of bismuth renaissance associated with the need to increase the effectiveness of H. pylori eradication therapy. Interest in bismuth preparations is also associated with their cytoprotective properties, since it is defects in cytoprotection that underlie a number of sufferings of the gastrointestinal tract (for example, NSAID-induced gastro- and enteropathies).

The gastroprotective effect is based on the ability of bismuth compounds to selectively bind to proteins on the damaged gastric epithelium, especially at the bottom of the ulcer, forming a protective layer against aggressive gastric contents [1, 2]. Bismuth salts, deposited on the gastric mucosa, interact with glycoproteins at the bottom of erosions and ulcers, creating a protective barrier against hydrochloric acid, pepsin, bile acids, pancreatic enzymes, alcohol and other aggressive substances [2, 3]. In addition, the effectiveness of bismuth salts is associated with a prostaglandin-mediated mechanism. It has been established that bismuth tripotassium dicitrate increases the synthesis and secretion of cytoprotective classes of prostaglandins, as well as prostaglandin-dependent bicarbonate production in the mucosa of the upper sections of the GIT, thus increasing the regenerative potential of the mucosa and increasing the buffer capacity of mucus [2, 4]. Bismuth salts also stimulate the production of epidermal growth factor in areas of damaged mucosa, which stimulates the growth of epithelial cells [2].

MATERIALS AND METHODS

The bactericidal properties of bismuth tripotassium dicitrate are associated with the inactivation of proteins and enzymes of H. pylori, including urease, catalase and lipase, which are key for the pathogen [1]. Interactions occur with cysteine-rich proteins and peptides in which bismuth replaces catalytic or structural metals such as iron, nickel and zinc [5]. When used in eradication therapy regimens, bismuth compounds have a synergistic effect with antibiotics by increasing the cytoplasmic pH of H. pylori bacteria, which makes them more sensitive to β-lactams and macrolides [1, 6]. In addition to the bactericidal effect, bismuth salts block the adhesion of H. pylori to epithelial cells [2]. The effectiveness and safety of bismuth compounds varies. Among all bismuth salts, the most popular in domestic medicine is bismuth tripotassium dicitrate as the most effective and safe compound. Of the bismuth preparations, it is bismuth tripotassium dicitrate that has the lowest MIC (minimum inhibitory concentration) values in relation to the bacterium H. pylori, and is also characterized by the greatest clinical efficacy in the treatment of helicobacteriosis [1].

RESULTS AND DISCUSSION

Currently, ten preparations of bismuth tripotassium dicitrate are registered in our country: the original drug De-nol® (Astellas) and nine generic drugs, including the drug Ulcavis® (KRKA). In this regard, it is advisable to briefly touch upon the problem of original and generic drugs, which is extremely relevant for modern medicine.

An original drug is a drug first developed by a pharmaceutical company, studied in preclinical and clinical studies in accordance with the principles of GCP (good clinical practice) and protected by a patent [7]. After the expiration of the patent protection of the original drug, which usually lasts 5–10 years, the right to produce this molecule can be acquired by other companies. If there is no original drug on the country's market, the first registered generic drug is considered as a reference, that is, a comparison drug for subsequent generics.

A generic medicinal product (generic medicinal product, generic) is a medicinal product produced in the same way as an already registered and sold original drug, in the same dosage, with the same method of administration and other characteristics and expected clinical effectiveness and without - danger corresponding to the original drug [7, 8].

Ideally, all drugs containing the same active substance should be characterized by similar pharmaceutical, pharmacokinetic (bioequivalence) and therapeutic equivalence. Pharmaceutical equivalence refers to the content of the same active substances in the same quantity and in the same dosage form [7, 8].

Bioequivalence (pharmacokinetic equivalence) is understood as similar bioavailability (rate and extent of absorption, maximum concentration, area under the pharmacokinetic curve) of two pharmaceutically equivalent drugs after administration in the same dosage [7, 8]. For drugs with low bioavailability, for example, bismuth tripotassium dicitrate, as well as for biosimilars, bioequivalence studies are not carried out.

When comparatively considering bismuth preparations, some of their pharmacological features should be taken into account. Thus, a complex double therapeutic effect can be achieved only by dissolving bismuth tripotassium dicitrate tablets in the stomach and uniformly distributing the colloidal substrate over the surface of the mucosa. This process is pH-dependent, so the precipitation of bismuth subcitrate occurs best at low pH; it is believed that

pH 3.5 is the optimal value for the formation of bismuth oxychloride and bismuth subcitrate precipitation [9]. Thus, the formation of a stable colloidal solution with sufficient precipitates of bismuth salts is key for bismuth-containing preparations. Based on the data presented, it becomes clear that the clinical effectiveness of bismuth tripotassium dicitrate may depend, among other things, on some technological and physicochemical properties of the tablet form of the drug.

A comparative analysis of the physical -chemical and structural properties of tablet forms of drugs containing bismuth tripotassium dicitrate: the original drug De-Nol® (Astellas) and the generic drug Ulcavis® (KRKA). The study analyzed and compared the appearance of the tablets, the crushing strength of the tablets, assessed the cross-sectional structure of the tablets, carried out scanning electron microscopy, Raman mapping, determined the release of ammonia from the tablets and the disintegration of the drug under static conditions.

Figure 1. Visual comparison of Ulcavis® tablets, 120 mg (KRKA) - the left tablet in the photo, and De-Nol®, 120 mg (Astellas) - the right tablet in the photo. UV: 5.63×.

Appearance and size of tablets. Appearance may indicate the quality of production of the drug. Inspection of the appearance of the tablet allows you to identify various defects, such as chips, cracks, delaminations, which can affect the pharmacokinetics and effectiveness of the drug. For example, defects in the tablet surface may affect drug stability in the GIT lumen. In addition, the appearance of tablets is a good indicator of the quality of not only the production process, but also packaging and transportation [10]. In addition, the visual characteristics of the tablet (shape, size, color, etc.) can have a significant impact on patient adherence to therapy.

The dosage forms of Ulcavis® and De-Nol® tablets are round and have a characteristic diameter. De-Nol® tablets are more convex on the upper and lower surfaces compared to tablets of the Ulcavis® dosage form. During a visual inspection of the Ulcavis® and De-Nol® tablets, it was found that all of them were intact, smooth and had a uniform color. There were no visible cracks, chips, or other signs of physical instability on the surface of the tablets.

Crushing strength of tablets. Crushing strength is an indicator of the mechanical strength of tablets. Suitable mechanical strength ensures the integrity of the tablet during the manufacturing process, packaging, storage, transport and patient use. Thus, only sufficient crush strength can guarantee that the tablet will remain undamaged when removed from the blister pack. On the other hand, crushing strength is also an important characteristic that determines the disintegration and solubility time of the tablet. Tablets that are too strong may not dissolve within the required period of time, which will affect the bioavailability of the drug [3]. To determine the mechanical properties of a tablet, the most commonly used test is the diametric crush test, which determines the force required to rupture or break the tablet. The crush strength of 40 Newtons is the minimum for most drugs [4]. During the instrumental analysis, the crushing strength of Ulcavis® tablets, 120 mg (KRKA) was 181 newtons, De-Nol® tablets, 120 mg (Astellas) - 178 newtons. Thus, both dosage forms sufficiently exceed

the required value of 40 Newtons and are not significantly different from each other.

Cross-sectional morphology of the tablet core and shell. The morphology of the core and shell of the Ulcavis® and De-Nol® dosage forms was studied using scanning electron microscopy on a cross section of coated tablets. Scanning electron microscopy is used to accurately characterize the morphology of the tablet shell and cross-section of the tablet core in terms of identifying small cracks, nanopores and adherent nanoparticles [5]. In addition to scanning electron microscopy, confocal Raman microscopy is used in the laboratory, providing information about the distribution of components in the tablet and performing their chemical identification. The distribution of components in the tablet, in particular homogeneity [6], determines stability, which subsequently affects the solubility of the drug not only in vitro, but also in vivo (in the GIT lumen)

Microscopic comparison of the two dosage forms revealed no significant differences in morphology. Thus, in the shell of the De-Nol® dosage form, a slightly larger number of micro- and macropores were detected, which may be due to different concentrations of TiO2 in the composition of the two dosage forms. Studies conducted using confocal Raman spectroscopy showed that the dosage forms of Ulcavis® and De-Nol® do not differ in the distribution of components. The comparability of the microstructure of two dosage forms is the key to the equivalence of their physicochemical properties. Disintegration of tablets under static conditions. Static analysis of the disintegration of bismuth tripotassium dicitrate preparations was carried out in a dilute solution of hydrochloric acid at pH 1.2. The disintegration of tablet forms under static laboratory conditions is not equivalent to disintegration in the dynamically changing environment of the stomach, however, this is the standard method when comparing two dosage forms. In fact, even the slightest change in the composition or structure of the tablet, the manufacturing process, storage and transportation conditions can affect the disintegration time in an acidic environment [7]. The predominant mechanisms of disintegration under static conditions are deagglomeration of particles, swelling of polymers and dissolution of tablet components [8].

During laboratory analysis, it was found that tablets of the Ul-Kavis® and De-Nol® dosage forms do not dissolve in 0.1 M HCl at 37 °C under static conditions. Both dosage forms swell and undergo erosion processes within 6 hours. The similarity of disintegration processes over a long period of time indicates the structural similarity of the two dosage forms Ulcavis® (KRKA) and De-Nol® (Astellas).

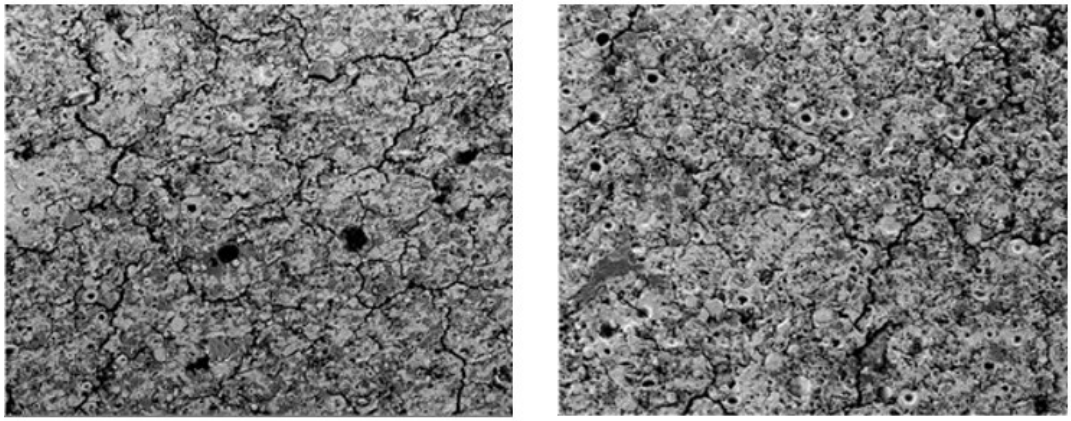

Figure 2. Cross-sectional scanning electron microscopy (SEM) images of 200x

magnification of the tablet core: A) 200x magnification of the tablet core of Ulcavis®, 120 mg D 57091 (KRKA); B) 200-fold increase in the core of the De-Nol® tablet, 120 mg 208052014 (Astellas);

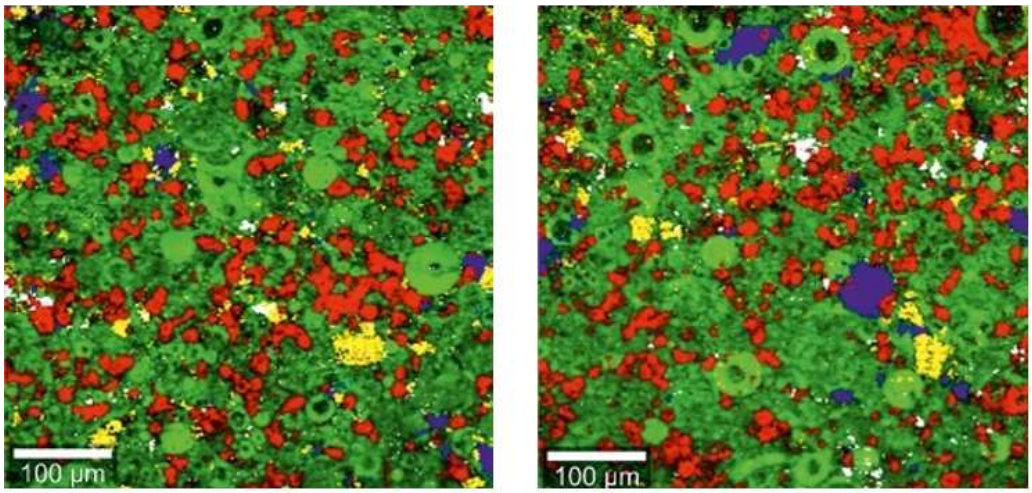

Figure 3. Raman mapping of the cross section of a 500 × 500 µm tablet (APS - green; starch - red; macrogol - blue; potassium polacrilin - yellow; magnesium stearate - white): A) Ulcavis®, 120 mg D 57091 (KRKA); B) De-Nol®, 120 mg 208052014 (Astellas).

Determination of ammonia release. The presence of ammonia in the structure of the tablet is usually required for adequate dissolution of the active substance.

During laboratory analysis, it was demonstrated that greater amounts of ammonia are released from De-Nol® tablets compared to Ulcavis® tablets under the same analytical conditions. Since ammonia released from the tablets can change the pH of the gastric juice, which can affect the process of formation of the colloidal substrate, additional analysis was carried out in laboratory conditions, demonstrating similar changes in the pH of the environment when the tablet forms of De-Nol® and Ulcavis were in them.

Decay analysis. Disintegration analysis is the most important laboratory comparative analysis of two dosage forms and has the greatest predictive value in terms of the clinical effectiveness of the drug.

There are various ways to test the disintegration of tablets. However, the main and preferred test is the disintegration assay, which uses standardized equipment to assess disintegration and follows the conditions specified by leading pharmacopoeias. For this parameter, the requirements of the European and Russian pharmacopoeia are identical. In accordance with the requirements of the European Pharmacopoeia of 2014 for film-coated tablets, the disintegration of Ulcavis® 120 mg and De-Nol® 120 mg tablets was analyzed in distilled water (6 tablets) and in 0.1 M hydrochloric acid (18 tablets) at a temperature of 37 ± 2 °C. To pass the test according to the requirements of the European and Russian Pharmacopoeia, it is necessary that all 6 tablets are dissolved in distilled water or that at least 16 of 18 tablets are completely dissolved in 0.1 M HCl within the prescribed time.

In table Figure 1 shows the results of dissolving drugs in two media. As can be seen from the presented results, all tested tablet forms of Ulcavis® 120 mg and De-nol® 120 mg dissolved within the prescribed time (no more than 15 minutes) in distilled water and 0.1 M HCl. Excipients. All excipients included in the dosage forms of Ulcavis® and De-nol® are

well-known compounds that have been used in tablet forms of various drugs for many years. Corn starch, macrogol, povidone, potassium polacrilin, magnesium stearate are generally considered non-toxic and non-irritating GIT substances [9].

Figure 4. Disintegration of dosage forms of Ulcavis® (KRKA) and Astellas® under statistical conditions at pH = 1.2: A) disintegration of dosage forms of Ulcavis® and De-Nol® at t = 0 h; B) disintegration of the dosage forms of Ulcavis® and De-Nol® at t = 6 h.

Table 1 Comparison of the disintegration of film-coated tablets, Ulcavis® and De-Nol® in purified water and in 0.1 M HCl (pH = 1.2)

	Units	Disintegration results (min:s)		Eligibility Criteria	Number of unacceptable results
		A drug; Series No.			
		Ulcavis®, film-coated tablets, 120 mg D 57091	De-Nol®, film-coated tablets, 120 mg 208052014		
Purified water	Average	05:03	04:55	Less than 15 minutes	0 of 6
0,1 M HCl	Average	06:03	04:58	Less than 15 minutes	0 of 6
	Average	05:44	05:28		0 of 6
	Average	06:17	05:38		0 of 6

TiO2 is also used as an auxiliary substance. The use of TiO2 is regulated by SanPin 2.3.2.1293–03 as a food additive E 171. According to data, titanium dioxide does not dissolve in gastric juice and is practically not absorbed by the body through the intestinal walls. Thus, titanium dioxide does not accumulate in tissues and is completely eliminated from the body [2]. This substance is widely used in food products as a food additive with code E 171, as well as in pharmaceutical dosage forms for topical and oral use [2]. According to the classification of the International Agency for Research on Cancer (IARC), TiO2 is a potentially carcinogenic substance for humans and belongs to group 2B [3]. However, this classification is based on toxicity test results obtained from two inhalation studies in rats, and not on carcinogenicity studies, which were all indisputably negative [4]. There have been no recent relevant studies confirming the carcinogenic potential of TiO2 after oral administration. A causal relationship of carcinogenicity associated with titanium dioxide has never been reported since titanium dioxide was introduced to the market more than 90 years ago.

Bismuth tripotassium dicitrate, in accordance with the instructions, is used to treat the following pathological conditions: peptic ulcer of the stomach and duodenum in the acute phase; chronic gastritis and gastroduodenitis in the acute phase, including those associated with H. pylori; irritable bowel syndrome, which occurs predominantly with symptoms of diarrhea; functional dyspepsia not associated with organic diseases of the GIT organs [4]. Moreover, in

clinical practice, bismuth tripotassium dicitrate is mainly used to treat the pathology of the upper sections of the GIT.

Epidemiological studies indicate that symptoms from the upper parts of the GIT are among the most common complaints in children and adults: for example, complaints of a dyspeptic nature occur in 25–40% of the population during their lifetime [5].

Organic and functional disorders in the upper parts of the GIT can lead to the development of dyspeptic complaints [3]. The etiopathogenesis of functional dyspepsia is based on motor disorders, excess acid production, changes in the visceral sensitivity of the gastric and duodenal mucosa, psychosocial factors [6, 7].

CONCLUSION

Bismuth preparations are basic drugs for the treatment of acid-dependent diseases of the upper sections of the GIT. Considering the high prevalence of acid-dependent diseases and Helicobacter pylori infection in the domestic population, the problem of the quality of tablet forms of bismuth tripotassium dicitrate registered in the Russian Federation seems particularly relevant at present.

U. Hudoklin et al., at a research center certified according to European standards in Novo Mesto (Slovenia), carried out a comparative analysis of the physicochemical and structural properties of tablet forms of drugs containing tripotassium bismuth dicitrate: original the drug De-Nol® and the generic drug Ulcavis®.

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