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EVALUATION OF BIOPHARMACEUTICAL AND PHARMACOLOGICAL PROPERTIES OF COMBINED TERNARY COMPONENTIAL ANALGESIC TABLETS

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ABSTRACT--*This study aimed to investigate the biopharmaceutical and the pharmacological features of the recommended combined tablets using in vivo and in vitro methodology. We previously developed technology obtaining combined ternary tablets with a potential analgesic effect. In vitro experimental analyses were performed on a Rotating Basket instrument included in the State Pharmacopoeia XI (SPh XI). Based on the results of studying the effect of pH on the dissolution rate of the recommended tablets, the use of an neutral medium - purified water is recommended for further studies. From a biopharmaceutical point of view, the basket rotation speed is 100 turnover per minutes. The acute toxicity of the compared drugs was studied by the generally accepted method described in the literature, a single administration with the determination of the toxicity class. The analgesic effect of the drug was studied on white outbred mice, in the amount of 18 animals, weighing 20-23 grams. A specific pain reaction - "cramps" (characteristic movements of animals, including contractions of the abdominal muscles, alternating with their relaxation, stretching of the hind limbs and flexing of the back) were caused by intraperitoneal administration of 0.75% acetic acid (0.1ml/10g body weight). The antipyretic effect of the drugs was evaluated in rats weighing 180-200 g. Body temperature excited by intravenous administration of Pyrogenal. The experimental study of the indicators of acute toxicity, and specific activity of the recommended combined tablets performed in comparison with the tablets Metamizole Sodium 500 mg tablets(under abrand name "Analgin").*

Key words--*Analgesic; Combined ternary componential (CTC) tablets; Metamizole sodium;*

I. . INTRODUCTION

Last decades, there has been a gradual enlargement in the interest of developers and manufacturers in the creation of combined medicines (fixed combinations) - medicines containing two or more active substances in one dosage form. This is due to the expected advantages of combined preparations compared to mono-componential ones (greater efficacy, accelerated onset of effect, greater safety and better tolerance with comparable efficacy) by virtue of the use of lower doses of one or more components of the combination, as well as ease of use (reducing the number of simultaneously taken tablets, simplification of the reception scheme). Combined drugs can simplify

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the procedure for their intake by the patient if the combination of active substances has already recognized as having the declared therapeutic characteristics [1,2,5].

In this regard, the study of preclinical studies of combination drugs is very relevant. Choosing the optimal clinical research strategy will provide sufficient information about the effectiveness and safety of the novel combined drug for its subsequent registration [3-6].

The main criterion for the quality indicator of the newly developed dosage forms is the conduct of biopharmaceutical studies in experiments "in vitro" and "in vivo". Among the primary issues of pharmacy, the leading ones are the expansion of the range of drugs and the improvement of the biopharmaceutical properties of existing ones. One of the biopharmaceutical criteria that determine the therapeutic efficacy of a drug substance is its bioavailability [4-6].

Bioavailability is an objective characteristic of therapeutic efficacy since the value of a drug ultimately lies on the manifestation of a therapeutic effect. One of the main biopharmaceutical characteristics is the solubility of the drug. It determines the possibility of creating a dosage form with an effective dose of the drug, the kinetics of its release from the dosage form, the speed, and completeness of absorption. A study of the bioavailability of drugs, preparations or their dosage forms usually begins with in vitro experiments and ends with in vivo experiments with further clinical investigation [7].

The aims of this study were to investigate pharmacological properties via method a specific pain reaction - “cramps” (in vivo) and biopharmaceutical properties of combined ternary analgesic tablets by method in vitro.

II. EXPERIMENTAL

2.1. Materials and Methods

Metamizole sodium (Analgin) was purchased from HEBEI JIHENG (GROUP) PHARMACEUTICAL CO., LTD, No. 368 Jianshe Street, Hengshui City, Hebei Province, 053000 P.R. China. Drotaverine hydrochloride and diphenhydramine hydrochloride were purchased from Xi’an Accenture Biological Technology Co., Ltd, Room703, Unit 1,No.1,Weilanchuncheng Residential Quarter, Taoyuan North Road 355, Lianhu District, Xi'an. As a comparison using "Analgin" - tablets (C: 32511017S.g: 11/2022 No. and date of registration DV / X 02159/09/16 23/09/16 B-250-95 45796 RUz 23/06/06), manufactured by Borisov Medical Products Plant OJSC, Belarus were purchased from a drug store "Tashkent Farm" LLC, 83, st. Shota Rustaveli, Yakkasaray district, Tashkent.

2.2. Materials

Solubility test (in vitro) of CTC analgesic tablets was carried out using the instrument "ERWEKA DT80" (Germany). Tableting is carried out on a tablet machine manufactured by Gaylord Pharma Sysrems, India. The number of nests on the matrix table 27. Productivity: 50-136 thousand tablets per hour.

2.3. Preparation of CTC tablets

Wet granulation is used to obtain tablets by which tablets are compressed from the granules of active ingredients (metamizole sodium, drotaverine hydrochloride and diphenhydramine hydrochloride) and suitable

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excipients. All the ingredients were passed through #60 mesh separately. Then the ingredients were weighed and mixed in geometrical order and granulated with 2% starch paste. Dried granules are pressed into tablets of 500 mg by using press tablet machine. 500 mg tablets are, 12 mm ± 0.2 mm in diameter, 3.2 mm ± 0.7 mm high, average weight 0.5 g ± 5%.

2.4. Determination of analgesic activity of CTC tablets

2.4.1. Animals

The analgesic effect of the drugs was studied on white outbred mice, in the amount of 18 animals, weighing 20-23 g.

2.4.2. Determination of analgesic activity of CTC tablets

A specific pain reaction is "cramps" (characteristic movements of animals, including contractions of the abdominal muscles, alternating with their relaxation, stretching of the hind limbs and arching of the back) caused by intraperitoneal administration of 0.75% acetic acid (0.1 ml / 10 g body weight) [8,9]. For this, white mice were divided into 3 groups of 6 animals each. The drugs were administered as follows:

Control group 1 - mice of this group were injected intragastrically with 0.4ml purified water + after 15 minutes intraperitoneally 0.75% acetic acid at a dose of 0.2 ml / 20g;

Experimental group 2 - mice were injected intragastrically with Analgin, produced by Borisov Plant of Medicinal Products OJSC, Belarus at a dose of 500 mg / kg (2.5% solution) + after 15 min intraperitoneally 0.75% acetic acid at a dose 0.2ml / 20g.

Experimental group 3 - mice were injected intragastrically with CTC tablets, developed at the Tashkent Pharmaceutical Institute, Uzbekistan at a dose of 500 mg / kg (22.5% solution) + after 15 min intraperitoneally 0.75% acetic acid at a dose of 0.2 ml / 20g;

Over the next 15 minutes after the injection, the number of writhing was calculated for each animal. The analgesic effect was evaluated by reducing the number of writhing as a percentage of control.

2.5. Determination of antipyretic activity of CTC tablets

2.5.1. Animals

The antipyretic effect of the drugs was studied in rats weighing 180–200 g.

2.5.1. Determination *of antipyretic activity of CTC tablets*

The ability of the compared drugs to reduce the increased body temperature caused by intravenous administration of Pyrogenal was investigated. For this, white rats were divided into 3 groups of 6 animals each [7,9]. The drugs were administered as follows:

Control group 1 - Pyrogenal was intravenous administered to rats of this group, and after 60 minutes, 2 ml of water was intragastrically administered.

Experimental group 2 - rats were injected intravenous with Pyrogenal at a dose of 4 mg / kg, and after 60 minutes, against the background of a febrile reaction, the drug Analgin at a dose of 500 mg / kg was administered.

Experimental group 3 - rats were injected intravenous with Pyrogenal at a dose of 4 mg / kg, and after 60 minutes, against the background of a febrile reaction, CTC tablets at a dose of 500 mg / kg was administered intragastrically.

Body temperature was measured rectally, 60 minutes after the administration of the compared drugs.

2.6. Statistical analysis

The results were statistically processed using the paired Student's criterion [10].

2.7. Study of the bioavailability of recommended CTC tablets in vitro experiments

It is known that some indicators affect the rate of release of the active substance: excipients, volume, and pH of the solvent, and rotation speed of the basket. The study was conducted taking into account the influence of various parameters, on the rate of release of active substances from tablets. In order to select the optimal pH of the solvent, solvents with different pH values were used. As a neutral, acidic, alkaline medium was used - purified water, 0.1 N hydrochloric acid (HCl) solution and 0.1 N sodium hydroxide solution, accordingly. In experimental studies, the volume of the solvent medium was standard - 1000 ml. When developing the "dissolution" test, the rate of release of biologically active substances, studies were conducted to establish the optimal speed of rotation of the basket. The tablets were dissolved at the following basket rotation speeds: 50, 100, 150, 200 turnover per minute. Every 15 minutes from the start of the experiment, samples were taken to quantify the active substances that transferred to the solvent medium. The determination of the quantitative content of active substances was carried out according to the methods of Normative Technical Document (NTD). For the scientific justification of the rational speed of rotation of the basket, the antilogarithms of the obtained values were calculated for the analyzed drug [12,13].

III. RESULT AND DISCUSSION

3.1. Analgesic activity of CTC tablets

The research results showed that after the introduction of acetic acid in mice of the control group, the number of writhing was 29.3 ± 2.16 times. In mice of the experimental group, which were administered CTT, the number of cramps was 7.5 ± 1,049, i.e., 74.4% less than in the control group. The results show a reliable analgesic effect of the CTC tablets, developed at the Tashkent Pharmaceutical Institute (Table 1).

Similar data were obtained when studying the analgesic effect of the drug "Analgin", produced by JSC "Borisov Plant of Medicinal Products", Belarus. The number of writhing in mice that were injected with Analgin, produced by Borisov Plant of Medical Products OJSC, Belarus, was 7.8 ± 1.8, which is 73.3% less than the indices of the control group (Table 1).

Table 1. Analgesic effect of CTC tablets and Analgin

Animal mass (g)	**Drugs**		

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	mg/kg	ml	**Acetic acid** 0,75 %	**The number of cramps after the introduction of acetic acid**	**The effect,**%
Control group + purified water					
21,8± 1,16	-	0,4	0,2	29,3 ±2,16	-
Analgin, Borisov Medical Products Plant OJSC, Belarus					
21,8 ± 0,75	500	0,4	0,2	7,8 ± 1,8 p<0,05	73,3
Combined ternary componential (CTC) tablets, developed at the Pharmaceutical Institute, Uzbekistan					
21,6 ± 1,0	500	0,44	0,2	7,5 ± 1,049 p<0,05	74,4

3.2. Antipyretic activity of CTC tablets

The research results showed that after administration of Pyrogenal in rats of the control group, after 60 minutes, an increase in body temperature to 39.2 ± 0.14 °C was observed. After administration of CTC preparation, after 60 minutes, a decrease in body temperature to 38.13 ± 0.2 °C was observed. Those. practically did not differ from the initial temperature (before the introduction of Pyrogenal) (P = 0,000) (Table 2).

Similar data were obtained when studying the hypothermic effect of the drug "Analgin" manufactured by Borisov Medical Plant OJSC, Belarus. 60 minutes after drug administration, the body temperature of the rats decreased to 38.15 ± 0.1 °C, which practically did not differ from the initial temperature (before the introduction of Pyrogenal) (P = 0,000) (Table 2).

Table 2. Antipyretic effect of CTC tablets and Analgin

Weight, **g**	**Dose** m**g/kg**	**Temperature body before the introduction of Pyrogenal,** ºC	**Temperature body after administration of Pyrogenal, ºC**	**Temperature body after drug administration, ºC**
Control group + purified water				
188 ± 4,5	-	37,8 ± 0,2	39,2 ± 0,14	39,2± 0,19
Analgin, Borisov Medical Products Plant OJSC, Belarus				
189,5 ± 5,9	500	38 ± 0,18	39,3 ± 0,16 P>0,05	38,15± 0,1 P<0,05
Combined ternary tablets (CTT), developed at the Pharmaceutical Institute, Uzbekistan				

191 ± 5,0	500	38 ± 0,2	39,4 ± 0,16 P>0,05	38,13± 0,2 P<0,05

3.3. In vitro study of the bioavailability of recommended CTC tablets

It can be seen from the data in Figure 1**Error! Reference source not found.**, the pH of the dissolving medium has an effect on the rate of release of active substances from the test tablets. Based on the results of studying the effect of pH on the dissolution rate of CTC tablets for further research, we recommended the use of a neutral medium – purified water. When developing the "Dissolution Test", the rate of release of biologically active substances, studies were conducted to establish the optimal rotation speed of the basket. The experiments were carried out at basket rotation speeds of 50, 100, 150, and 200 rpm (as shown in Figure 2). From the figure it is seen that the release of the active substance from CTC tablets at various speeds of rotation of the basket occurs intensively.

It should be noted that at a basket rotation speed of 100 rpm, the concentration of active substances that have passed into the solution in 45 minutes is more than 75%, which meets the requirements of the State Pharmacopoeia XI (SPh XI), which proves that under such conditions, the kinetics of the release of the active substance according to the first-order equation is observed. Also, the results show that the dissolution rate of the tablets has a directly proportional relationship with the speed of rotation of the basket.

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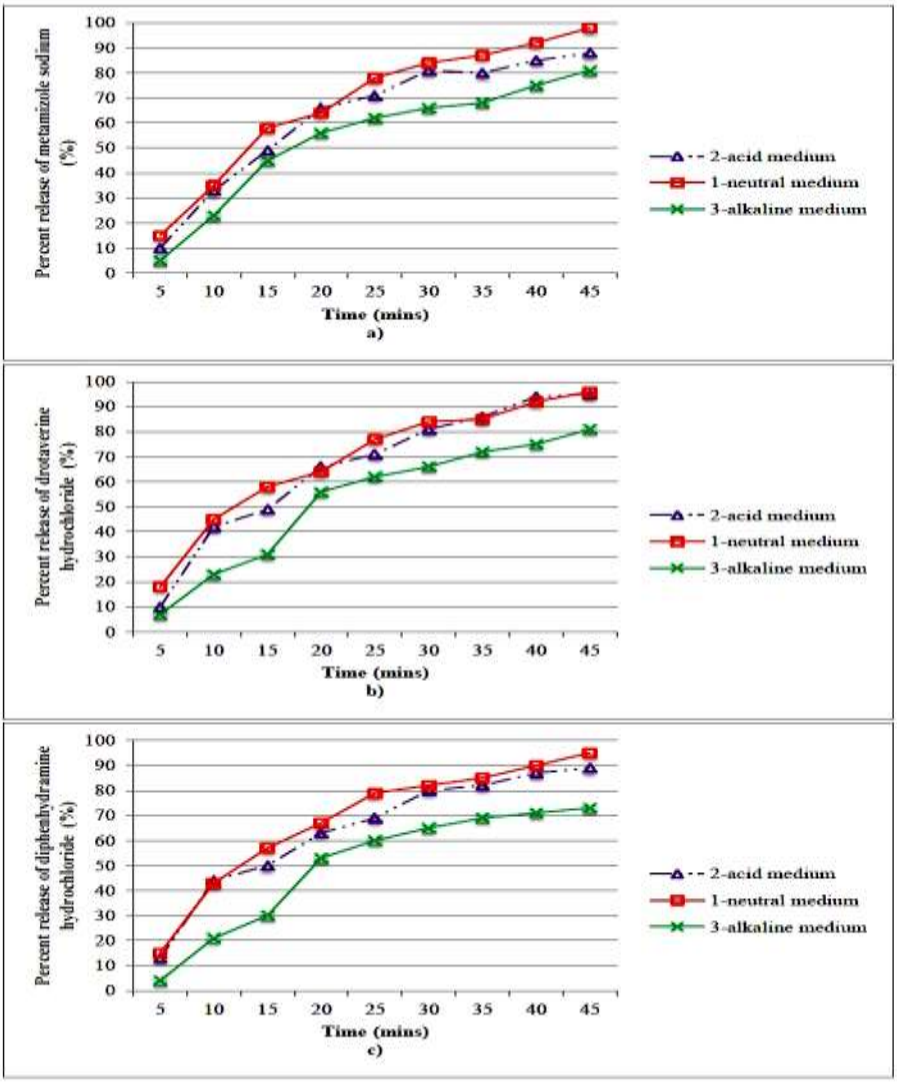

Figure 1. The results of a study of the effect of pH of a solvent on the dissolution rate of active subtances of CTC tablets

a) Metamizole sodium

b) Drotaverine hydrochloride

c) Diphenhydramine hydrochloride

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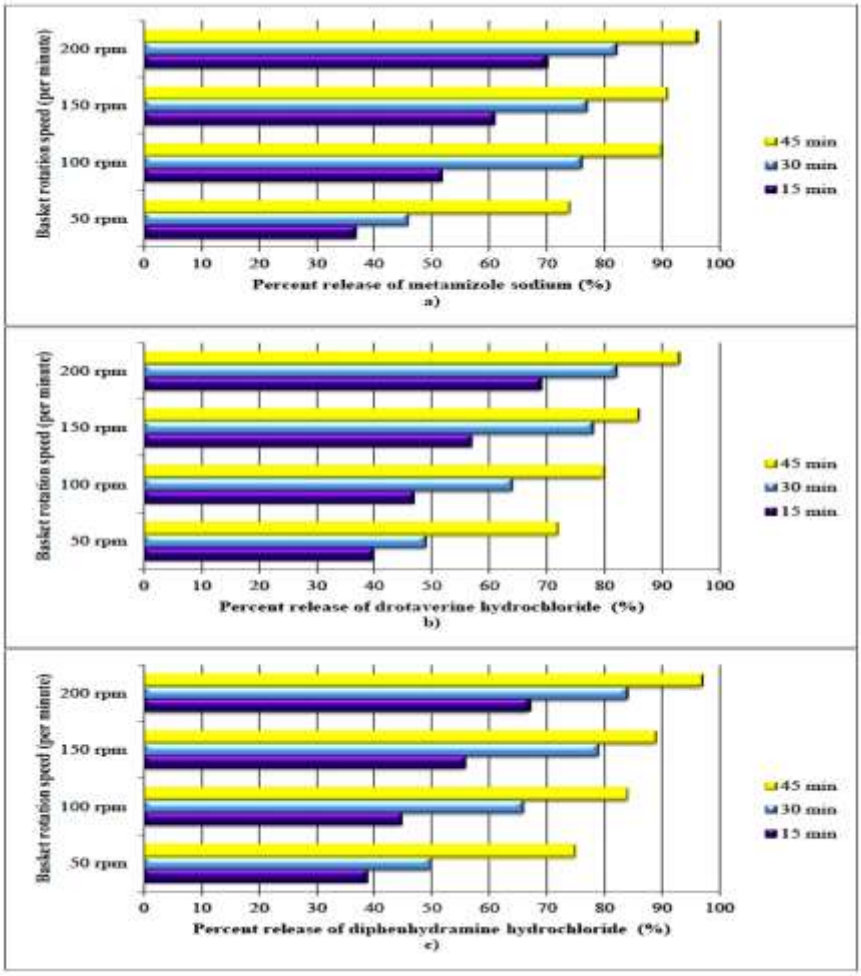

Figure 2. Results of studying the influence of basket rotation speed on the intensity of the release of active substances from CTC tablets

a) Metamizole sodium

b) Drotaverine hydrochloride

c) Diphenhydramine hydrochloride

IV. CONCLUSIONS

Thus, the data obtained show that the studied CTC tablets in comparison with the drug "Analgin", has a reliable analgesic effect and significantly reduces the body temperature of white rats caused by intravenous administration of Pyrogenal, i.e. have the equivalent hypothermic effect. Based on the foregoing, on the basis of the results of experiments to study the effect of pH on the dissolution rate of CTC tablets for further research, we recommended the use of a neutral medium – purified water and a basket rotation speed of 100 rpm. Based on the foregoing, for further research on the quality of finished products from a biopharmaceutical point of view, it is recommended that the basket rotate at 100 rpm, the volume of which is dissolved among 1000 ml.

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