USING THE HACCP METHOD IN QUALITY RISK MANAGEMENT IN THE PRODUCTION OF OROMUCOSAL GEL

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Introduction

With the adoption in the EU of the regulatory document of the European Medicines Agency (European Medicines Agency) EMA / INS / GMP / 79766/2011 "Quality Risk Management (ICH Q9)"separate guidance was issued in Ukraine in 2011 - Instruction ST-N MOH 42-4.2: 2011 "Medicines. Quality Risk Management (ICH Q9)".

Pharmaceutical industry and regulatory bodies professionals can assess and manage risk using recognized risk management tools and / or internal techniques (e.g., standard working methods). The most commonly used risk management tools include: Failure Mode Effects Analysis (FMEA), Failure Mode, Effects and Criticality Analysis (FMECA), Fault Tree Analysis (FTA), operational safety analysis and Hazard Analysis and Critical Control Points (HACCP), as well as the basic supporting risk management methods for flowcharts, control charts, etc. [1].

Using the species and impact analysis (FMEA) method, risk factors were identified during the pharmaceutical development phase of the drug "Fenspiride hydrochloride, coated tablets, 0.08 g". Risk factors were ranked based on priority risk number (PRN) according to the Pareto diagram. The Pareto analysis showed that the most critical are the following risk factors: tablet size, bulk density of powdered tablet mass during tableting, bulk density of granulate after calibration [2].

Using the HACCP method, the analysis of dangerous factors that may affect the quality of the dosage form "Chondroitin sodium sulfate, injection solution 100 mg / ml in ampoules of 2 ml". For each potentially dangerous factor, the probability of its occurrence was estimated. Critical stages of the technological process and critical control points were identified; set critical limits for each checkpoint; a monitoring system for control points has been developed [3].

Using the method of cause and effect analysis, the potential factors that have the most significant impact on the quality of "Niavit, solution for injection", in terms of mechanical inclusions, were identified. Critical quality parameters of the initial components and properties of the product have been identified, the most likely risks to the quality of the preparation have been identified, analysed and evaluated [4].

Application of general principles and approaches of the Guideline "Medicines. Quality Risk Management (ICH Q9)"at the stage of pharmaceutical development, using appropriate risk management tools both in general to the manufacture of medicines and to individual processes is an effective measure of quality assurance for the developed medicinal product.

A necessary element of pharmaceutical development under the principle of "Quality by design" (QbD) is a general risk assessment, which is expressed in the relationship of the characteristics of materials and process parameters with critical indicators of the quality of the drug [5].

Despite the general approach, plans for pharmaceutical development experiments, quality targets, critical quality indicators and critical process parameters will be dramatically different for drugs in different dosage forms, as well as for different drugs in the same dosage form that should be considered when planning each development and each technology transfer [6, 7].

The technology of the combined dental gel was developed taking into account its properties as a dispersed system, as well as the properties of the active and auxiliary substances that are part of it. In order to manage quality risks effectively, it is necessary to have data about the sustainability of the process. Critical process parameters that need to be managed or monitored to ensure the required quality of the drug should be identified and specified.

The aim of the work was to identify, through one of the risk management tools, the HACCP method, potential factors that may affect the quality of a combined dental gel containing metronidazole benzoate, miramistin, hyaluronic acid. It was necessary to analyse the developed technology and production scheme, identify critical control points, criteria for their acceptability, develop corrective and preventive actions when the parameter goes beyond the limits, and evaluate the possible risk to quality.

Materials and methods

The subject of the study was the technology and technological scheme of the production of a combined gel for the treatment of infectious diseases of the mucous membrane of the mouth and gums. Hazard Analysis and Critical Control Points (HACCP) were used to evaluate and manage risks in the manufacture of the new drug. The HACCP method is a structured method for identifying hazards and establishing control measures at all stages of the process to prevent hazards and maintain product quality and safety.

The HACCP tool, the "Decision tree", was used to establish critical control points. The standard "Decision tree" consists of questions that make it possible to decide whether a production process control point is critical to managing a potential hazard.

Results and discussion

An expert group of experts conducted an analysis and evaluation of the danger of individual stages of the technological process and determination of the criticality of the controlled parameters. The group consisted of qualified specialists from the pharmaceutical development department, thefactoryworkshop for the production of soft medicines, the quality control department. Expert team members are theoretically and practically aware of the use

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of quality risk management tools, in particular the HACCP method.

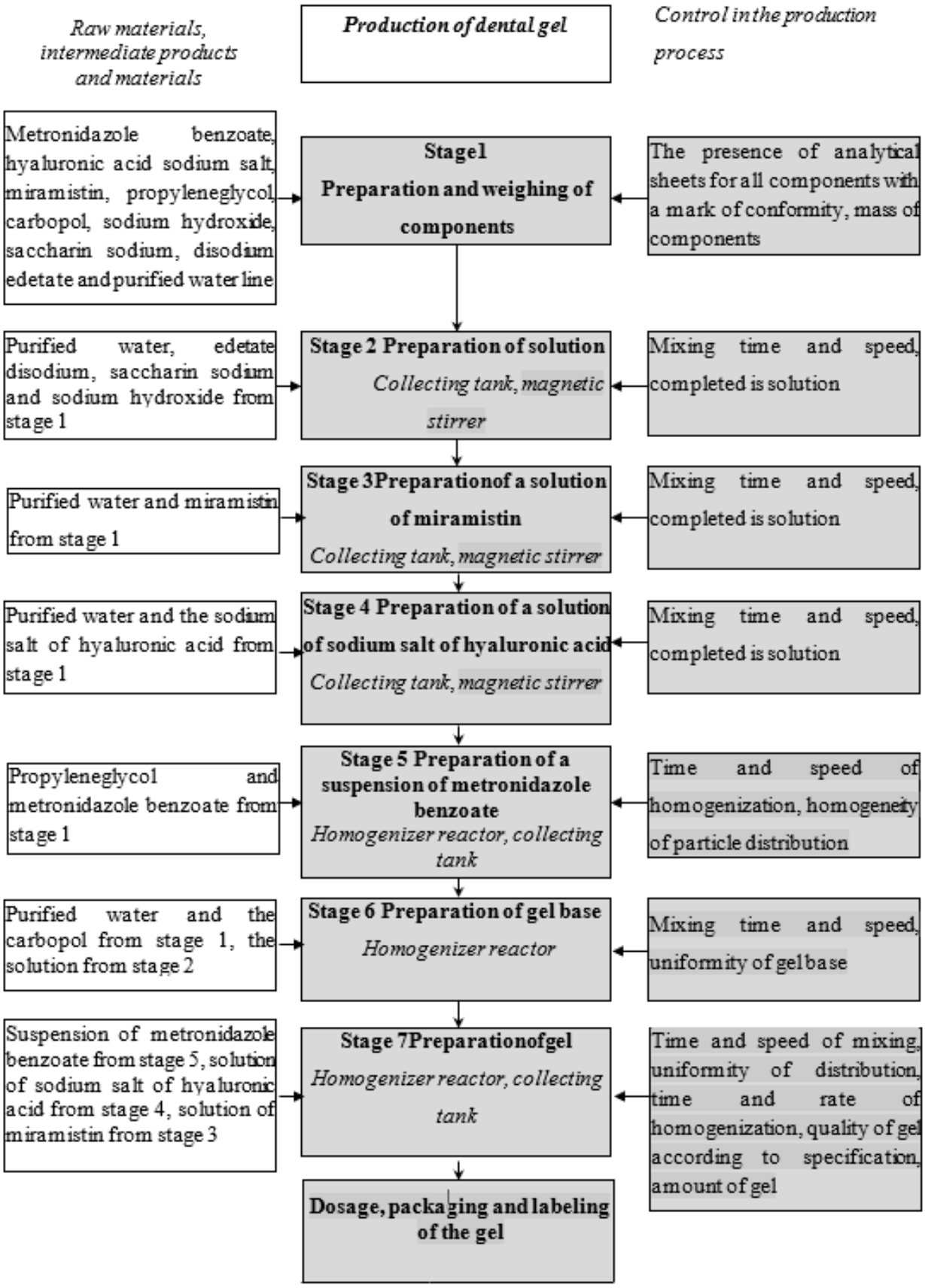

Fig. 1 . Flow chart of production of combined dental gel

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Analysis of the technological scheme of production of combined dental gel, which is shown in figure 1, showed that the production process consists of the general stages that are present in any technological process of drug production.

Sanitary preparation for production, marking and packaging of finished products are stages that are standard and not directly related to technology.

Almost all stages of the dental gel manufacturing process are critical and marked in grey. Using the tool "Decision tree", we identified the critical control points of the technological process of gel production, and set the eligibility criteria. The results of the studies are shown in table 1.

Table 1. Critical stages, critical control points (process parameters) and acceptability criteria for dental gel manufacturing technology

Critical stages	Critical parameters	Acceptability criteria
Stage 1 Preparation and weighing of components	accuracy of weighing of components	Ensures the correct selection of scales with the required measurement limits and accuracy of weighing
	mass of components	According to the production recipe and production protocol of the series
	input control of raw materials	Availability of analysis protocols and manufacturing authorization
Stage 2 Preparation of solution for neutralization	mixing time	20÷25 min
	the rotational speed of the mixer	300÷500 rpm
	completeness of dissolution	the solution should be transparent
Stage 3 Preparation of miramistin solution	mixing time	15÷25 min
	the rotational speed of the mixer	300÷500 rpm
	completeness of dissolution	the solution should be transparent
Stage 4 Preparation of a solution of sodium salt of hyaluronic acid	mixing time	20÷30 min
	the rotational speed of the mixer	300÷500 rpm
	completeness of dissolution	the solution should be transparent
Stage 5 Preparation of a suspension of metronidazole benzoate	homogenization time	5÷10 min
	the speed of rotation of the homogenizer	3000÷4000 rpm
	completeness of dispersion	the absence of non-dispersed particles
Stage 6 Preparation of gel base	mixing time	30÷35 min
	the rotational speed of the mixer	50÷60 rpm
	completeness of dispersion	the absence of non-dispersed particles
	mixing time	50÷60 min
	the rotational speed of the mixer	20÷30 rpm
	the uniformity of the gel	the gel should be homogeneous
Stage 7 Preparation of gel 7.1 Adding a suspension of metronidazole benzoate	mixing time	20÷30 min
	the rotational speed of the mixer	50÷60 rpm
	distribution uniformity	the gel should be homogeneous
7.2 Adding a solution of hyaluronic acid sodium salt	mixing time	20÷30 min
	the rotational speed of the mixer	50÷60 rpm
	distribution uniformity	the gel should be homogeneous

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Critical stages	Critical parameters	Acceptability criteria
7.3 Adding a solution of miramistin	mixing time	20÷30 min
	the rotational speed of the mixer	50÷60 rpm
	distribution uniformity	the gel should be homogeneous
7.4 Homogenization	homogenization time	5÷10 min
	the speed of rotation of the homogenizer	3000÷4000 rpm
	the homogeneity of the suspension	the gel should be homogeneous
	the quality of the gel	as required by the specification
Stage 8 Gel dosage	setting the dosage value	10.4 each
	the mass of the contents of the tube	not less than 10 g
	control of the appearance of the tubes	no mechanical damage, dirt on the tubes
	tightness control of tubes	must be hermetically sealed
	quality control of the gel in the tubes	as required by the specification
	control of storage conditions	do not store above 25 ° C

Risk factors were evaluated on the basis of two indicators: the likelihood of a hazard factor and the degree of risk created by that factor. The likelihood of a risk factor was as follows:

- unlikely - 1 time / month to 1 time / year;
- quitelikely - 1 time / week to 1 time / month;
- probably - 1 time / day up to 1 time / week;
- very likely - more than 1 time / day.

The degree of risk was assessed on a ten-point scale, where 0 is no risk, 1-4 is low risk, 5-6 is medium risk, 7-9 is high risk, 10 is very high risk.

During the processing of the gel technology, certain critical control points were monitored with the aim of developing preventive and corrective actions in case of their fall outside the eligibility criteria. The risk factors and the steps taken to address them are listed in table 2.

Table 2. Risk factors and preventive actions in combined dental gel production

Name of critical operation	Risk factors	The likelihood of a risk factor	Risk description	Preventive and corrective measures	Degree of risk
Input control of raw materials	Microbiological	unlikely	Microbiological contamination of raw materials	Control of storage conditions, control of conformity of packing to requirements of specification, control of terms of storage of raw materials	2
	Chemical	unlikely	Raw material mismatch to specifications		3
Weighing of active and auxiliary substances	Physical	unlikely	The mismatch of the mass of raw materials of technological documentation	Control of weighing, check of terms of metrological scales, control re-weighing of weighed quantity	4
Preparation of solutions	Chemical	unlikely	Mismatch of technological documentation to preparation mode	Control of the solution preparation mode	6

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Preparation of metronidazole suspension	Physical	quite likely	The suspension particles exceed the maximum allowable size	The use of the micronized substance metronidazole benzoate, control of homogenization mode	7
	Chemical	unlikely	Excess content of admissible impurities	Temperature control	5
Preparation of gel base	Physical	quite likely	The heterogeneity of the gel base	Control of the time of swelling of the gel and the mixing mode after neutralization	7
Preparation of gel	Physical	quite likely	The heterogeneity of the distribution of active substances in the gel	Mixing mode control	7

As can be seen from table 2, in the process of gel production, risk (physical factor) at the stages of metronidazole suspension preparation, preparation of gel base and gel directly is "Quite likely". "Unlikely" occurrence of a dangerous factor at such stages as the weighing of active and auxiliary substances, the preparation of solutions and during the input control of raw materials. The risk level of each factor, ranging from 2 to 7 points, was determined and corrective and preventive actions were developed for all critical control points to prevent risks to the quality of the medicinal product.

Conclusions

On the basis of the data obtained in the development of dental gel technology and using scientific knowledge and methodology of risk assessment by the method of HACCP, an analysis of technological scheme of its production was carried out. Process risks have been identified, critical control points have been identified and their allowed limits. For each control parameter, the probability of occurrence and the degree of risk were determined, and measures were proposed to prevent or eliminate the effects of the risk. The results obtained will then be used for the overall risk assessment of the quality of the new drug and validation of the technological process of its production.

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Introduction. With the adoption in the EU of the regulatory document of the European Medicines Agency (European Medicines Agency) EMA / INS / GMP / 79766/2011 "Quality Risk Management (ICH Q9)"separate guidance was issued in Ukraine in 2011 - Instruction ST-N MOH 42-4.2: 2011 "Medicines. Quality Risk Management (ICH Q9)". Pharmaceutical industry and regulatory bodies professionals can assess and manage risk using recognized risk management tools and / or internal techniques (e.g., standard working methods).Application of general principles and approaches of the Guideline "Medicines. Quality Risk Management (ICH Q9)"at the stage of pharmaceutical development, using appropriate risk management tools both in general to the manufacture of medicines and to individual processes is an effective measure of quality assurance for the developed medicinal product. The technology of the combined dental gel was developed taking into account its properties as a dispersed system, as well as the properties of the active and auxiliary substances that are part of it. In order to manage quality risks effectively, it is necessary to have data about the sustainability of the process. Critical process parameters that need to be managed or monitored to ensure the required quality of the drug should be identified and specified. **Materials and methods of the research.** The subject of the study was the technology and technological scheme of the production of a combined gel for the treatment of infectious diseases of the mucous membrane of the mouth and gums. Hazard Analysis and Critical Control Points (HACCP) were used to evaluate and manage risks in the manufacture of the new drug. The HACCP tool, the "Decision tree", was used to establish critical control points. **Results of the research and discussion.** An expert group of experts conducted an analysis and evaluation of the danger of individual stages of the technological process and determination of the criticality of the controlled parameters. The group consisted of qualified specialists from the pharmaceutical development department, thefactoryworkshop for the production of soft medicines, the quality control department. Analysis of the technological scheme of production of combined dental, showed that almost all stages of the dental gel manufacturing process are critical and marked in grey. Using the tool "Decision tree", we identified the critical control points of the technological process of gel production, and set the eligibility criteria. Risk factors were evaluated on the basis of two indicators: the likelihood of a hazard factor and the degree of risk created by that factor. The likelihood of a risk factor was as follows:

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unlikely, quitelikely, probably, very likely. The degree of risk was assessed on a ten-point scale. During the processing of the gel technology, certain critical control points were monitored with the aim of developing preventive and corrective actions in case of their fall outside the eligibility criteria. in the process of gel production, risk (physical factor) at the stages of metronidazole suspension preparation, preparation of gel base and gel directly is “Quite likely”. “Unlikely” occurrence of a dangerous factor at such stages as the weighing of active and auxiliary substances, the preparation of solutions and during the input control of raw materials. The risk level of each factor, ranging from 2 to 7 points, was determined and corrective and preventive actions were developed for all critical control points to prevent risks to the quality of the medicinal product. **Conclusions.** Based on the data obtained in the development of dental gel technology and using scientific knowledge and methodology of risk assessment by the method of HACCP, an analysis of technological scheme of its production was carried out. Process risks have been identified, critical control points have been identified and their allowed limits. For each control parameter, the probability of occurrence and the degree of risk were determined, and measures were proposed to prevent or eliminate the effects of the risk.

Keywords: quality risks, HACCP method, technological process, control critical points, dental gel.

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