**MINISTRY OF HEALTH OF THE REPUBLIC OF UZBEKISTAN**
**TASHKENT PHARMACEUTICAL INSTITUTE**

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# UNIFICATION OF METHODS FOR STANDARDIZATION OF SUSPENSION CONTAINING METAL HYDROXIDES

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Effective control over the quality of manufactured drugs, which include drugs containing metals, is required. Therefore, the issue, in turn, makes increased demands on the quality control of medicines and the improvement of quantitative determination methods, the development of new, more advanced analytical methods that allow the determination of medicinal substances with high accuracy and selectivity in wider ranges of determined concentrations with low material costs. When choosing an instrumental method for drug control, a number of requirements are taken into account: the ability to determine traces of organic substances in the sample with a minimum error, sufficient selectivity, the absence of a complicated sample preparation procedure, the possibility of automating the method, the minimum possible research time, sufficient versatility (the possibility of multielement analysis), minimum weight and size of equipment. The ongoing research is aimed at increasing the seriality and rapidity of the analyzes.

This monograph, to a certain extent, serves to fulfill the tasks established by the Decree of the President of the Republic of Uzbekistan dated April 10, 2019 No. UP-5707 "On further measures to accelerate the development of the pharmaceutical industry of the republic in 2019 - 2021".

The monograph provides information on the known methods of quality control of preparations containing aluminum and magnesium hydroxides in various dosage forms produced by the pharmaceutical industry of the Republic, the study of the pharmaceutical bioequivalence of a suspension containing aluminum and magnesium hydroxides. study of the biological bioequivalence of a suspension containing aluminum and magnesium hydroxides using the “Dissolution test” criterion. development of improved quality control procedures for a suspension containing aluminum and magnesium hydroxides, validation of quality control procedures for a suspension containing aluminum and magnesium hydroxides.

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# INTRODUCTION

## CHAPTER I. LITERATURE REVIEW

### 1.1. Modern aspects of quality control of suspension drugs.

Suspensions are a liquid dosage form containing, as a dispersed phase, one or more ground powdery substances distributed in a liquid dispersion medium. The size of solid particles in suspensions can vary within wide limits: in thin suspensions - within 0.1-1 microns, in coarsely dispersed - more than 1 micron.

There are suspensions for internal, external and parenteral use. Suspensions for parenteral administration are administered intramuscularly only.

Suspensions are formed in the following cases: substances that are not soluble in a liquid dispersion medium are prescribed. For example, substances such as sulfur and camphor are insoluble in water; the solubility limit of substances is overestimated, for example, in water - boric acid in a concentration of more than 5%, sodium tetraborate - more than 8%; assigned substances, separately readily soluble in water, but forming insoluble compounds upon interaction. For example, when zinc sulfate and lead acetate react in a solution, an insoluble compound is formed - lead sulfate, which is released in the form of the smallest powder; as a result of solvent replacement, for example, the addition of galenic and novogalenic agents to mixtures.

Suspensions are all-round free dispersed systems. They are characterized by the following properties: a) these are turbid systems not only under side illumination, but also in transmitted light. They give Tyndall's cone; b) there is no osmotic pressure; c) Brownian motion is weakly expressed, diffusion is not detected. The State Fund of the Republic of Belarus has a general article "Suspensions". In accordance with the State Fund of the Republic of Belarus, volume III, the rules for the preparation of suspensions have been developed.

Serious attention is paid to the quality of medicines (drugs) at the state level, because we are talking about the life and health of millions of people. The quality control system is headed by the Department of State Control of the Efficiency and Safety of Medicines and Medical Equipment of the Ministry of Health of Uzbekistan. The

quality standards of drugs are specified in the state standards and pharmacopoeial articles of the enterprise for a specific drug.

Drug quality control includes sampling, testing, checking for compliance with the requirements of specifications, as well as procedures for organizing, documenting and issuing a release permit.

The purpose of quality control is to prevent the sale of products that do not meet the established requirements - registration dossier, clinical trial protocol and product specifications.

The solution of quality control problems is provided by pharmaceutical analysis, which is carried out through the use of various research methods: physical, physicochemical, chemical and biological. The conditions and methods for conducting pharmacological analysis are regulated by the State Pharmacopoeia of Uz.

Physical and physicochemical methods require the use of appropriate devices and instruments, therefore they are also called instrumental or instrumental. Physical methods are based on measuring physical parameters - transparency, turbidity, color, moisture, melting point, solidification, boiling, and so on.

Physicochemical - measure the physical parameters of the analyzed system, which change as a result of chemical reactions. These methods include optical, electrochemical, chromatographic.

In chemical evaluation, the analysis is based on the course of chemical reactions. The biological method of quality control of medicines is used when it is impossible to draw a conclusion about the good quality of the drug using physical and chemical methods, or these methods are not sensitive enough to determine small amounts of highly active substances. In this case, tests are carried out on animals, individual isolated organs and groups of cells, as well as on certain strains of microorganisms by comparing the action of the tested and standard samples. Through the use of living organisms, as a result of research, it is possible to obtain direct information about the biological activity of various substances. In the structure of each manufacturer of medicinal products, a quality control unit should be organized, including a laboratory. The head of this structure must have the appropriate qualifications and work experience, since he is

responsible for the entire range of work to build an effective quality control system at the enterprise in accordance with applicable law.

The following requirements are imposed on the personnel involved in drug quality control:

1.the presence of higher education in the field of activity,

2. regular professional development, including passing refresher courses at least once every five years.

(Orders of the Ministry of Labor and Social Protection of the Russian Federation No. 429n and 431n).

## 1.2. Determination of pharmaceutical equivalence of drugs

Pharmaceutical equivalence - the equivalence of the reproduced drug in terms of the qualitative and quantitative composition of the original drug, ie: - in the composition of active substances; - by the strength of the action or concentration of active substances; - by the identity of dosage forms; - by the method of administration. BUT, the pharmaceutical equivalent may differ from the original in such characteristics as: spatial configuration, elimination mechanism, composition of excipients (dyes, flavorings, preservatives), shelf life.

Medicines are considered pharmaceutical equivalents if they contain the same active ingredient (s), have the same dosage form, route of administration, and are the same in strength or concentration. Pharmaceutically equivalent formulations are designed to contain the same amount of active ingredient in the same dosage form and must meet the same or pharmacopoeial or other applicable standards (i.e. strength, quality, purity, and determinability). However, the pharmaceutical equivalent may differ from the original in such characteristics as: spatial configuration, elimination mechanism, composition of excipients (dyes, flavors, preservatives), shelf life.

The ultimate goal of drug policy in any country in the world is to provide the population with safe, effective, high-quality and affordable drugs. One of the key points in this policy is the widespread use of generic drugs. Most often generics are used for socially significant diseases with a high prevalence (arterial hypertension, chronic heart failure, tuberculosis, diabetes mellitus, etc.). In this regard, it is obvious that a favorable effect on the course and outcome of socially significant diseases can be achieved only with the use of relatively affordable and high-quality generics.

According to the WHO definition, the term "generic" means a drug used in medical practice interchangeably with an innovative (original) drug, produced, as a rule, without a license from the creator company and sold after the expiration of the patent or other exclusive rights.

A generic drug must meet the following criteria [39]:

• contain the same active ingredient as the original product;

• have similar bioavailability;

• be produced in the same dosage form;

• maintain quality, efficiency and safety;

• have no patent protection;

• have a lower cost compared to the original drug;

• comply with pharmacopoeial requirements, produced under GMP (Good Manufacturing Practice) conditions;

• have the same indications for use and precautions.

As clinical practice shows, drugs containing the same active ingredients in the same pharmaceutical forms and doses, but produced at different enterprises, can differ significantly both in therapeutic efficacy and in the frequency of adverse reactions provided for in the instructions for their medical use.

EU Directive 2001/83 also defines essentially similar products. A medicinal product is essentially analogous to the original product if it meets the criteria of the same quantitative and qualitative composition with respect to active substances, the same dosage form and is bioequivalent, unless it is scientifically obvious that it differs from the original product regarding safety and effectiveness.

One of the main issues for both the doctor and the patient is the problem of interchangeability of generic and original drugs.

The international community, national health services are interested in the development and implementation into practice of scientifically based criteria for assessing the effectiveness and safety of generic drugs produced by various companies.

According to modern concepts, the compliance of a generic and a drug-brand is based on three essential components, designated as pharmaceutical, pharmacokinetic and therapeutic equivalence.

In European countries, it is considered that medicinal products are pharmaceutically equivalent if they contain similar active substances in the same amount and in the same dosage form, meet the requirements of the same or similar standards.

According to the American definition, pharmaceutically equivalent medicinal products contain the same active ingredients in the same dosage form, are intended for the same

route of administration, and are identical in strength of action or concentration of active substances.

However, pharmaceutically equivalent agents will not necessarily be therapeutically equivalent, i. E. those, after the use of which in the same molar dose, the effect from the point of view of efficacy and safety is virtually the same. Thus, when intravenously administered in the Russian Federation, erythromycin, registered in the Russian Federation, caused thrombotic complications with a high frequency, while in European countries, Abbott's erythromycin is widely used for intravenous administration, being considered the safest macrolide antibiotic for intravenous infusion.

Excipients play an important role in the safety of drug use. When creating generic drugs, it is necessary to require the preservation of the original composition of the excipients, which, however, is not always known.

The use of auxiliary ingredients in generic drugs is regulated on the basis of WHO recommendations [35, 36].

When assessing pharmacokinetic equivalence (or bioequivalence), the characteristics of absorption and distribution of drugs in the human body are compared. According to the WHO definition, “two medicinal products are considered bioequivalent if they are pharmaceutically equivalent, have the same bioavailability and, when administered in the same dose, provide adequate efficacy and safety”.

The definitions used in the countries of the European Union (EU) and the United States are slightly different.

According to the European formulation, two medicinal products are bioequivalent if they are pharmaceutically equivalent or alternative and if their bioavailability (rate and extent of absorption) after administration at the same molar dose is similar to such an extent that their efficacy and safety are substantially the same.

According to the American definition, bioequivalent drugs are pharmaceutically equivalent or pharmaceutically alternative drugs that have comparable bioavailability when tested under similar experimental conditions.

1.3. Determination of the biological equivalence of drugs.

Bioequivalence is the equivalence of a reproduced drug with an original drug in terms of pharmacokinetic parameters, i.e. Two drugs are recognized as bioequivalent if they have the same degree and rate of absorption, distribution and withdrawal of drugs from the body under equal experimental conditions.

• WHO “Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability”, 2005) “Two medicinal products are considered bioequivalent if they are pharmaceutically equivalent, have the same bioavailability and, when administered at the same dose, provide adequate efficacy and safety”.

• EMA "Note for guidance on investigation of bioavailability and bioequivalence", 2000 two medicinal products are bioequivalent if they are pharmaceutically equivalent or alternative if their bioavailability (rate and extent of absorption) after administration in the same molar dose is similar to such an extent that their efficacy and security are basically the same.

• Orange book, FDA bioequivalent drugs are pharmaceutically equivalent or pharmaceutically alternative drugs that have comparable bioavailability when tested under similar experimental conditions

• Russia, "... two medicinal products are bioequivalent if they provide the same bioavailability of the medicinal product." - Bioavailability, in turn, reflects the amount of unchanged active substance reaching the systemic circulation (degree of absorption) relative to the initial dose of the drug.

A bioequivalence study is essentially (for orally administered drugs) a test of comparative bioavailability. For each investigational drug, the main pharmacokinetic parameters characterizing the completeness of absorption should be determined: the area under the concentration-time curve (AUC), the absorption rate (Cmax, Tmax) and the rate of excretion of the active substance (Kel, T1 / 2). To conclude that there are no differences in these parameters, analysis of variance is applied and 90% confidence intervals are calculated. To confirm equivalence, it is required that the 90% confidence intervals for the bioavailability parameters of the study drug do not go beyond -80 and + 125% of the reference drug parameters.

It is important to note that one cannot talk about the bioequivalence of drugs if it is not known for sure where and how the drug was produced. If there is no certainty that the production site where this drug is produced complies with GMP requirements, it is pointless to study bioequivalence, like other clinical trials, because the quality of drugs is not maintained from batch to batch. In a global sense, GMP is a step-by-step, systematic step-by-step "embedding" of quality into a drug. In this regard, the study of bioequivalence is only a matter of the general system of quality assurance of medicines. All generics must have proven bioequivalence, since, in theory, only bioequivalent drugs can have similar clinical efficacy and safety profiles.

In 1984, the President of the United States signed a law requiring the FDA (Food and Drug Administration) to make the list of approved prescription and over-the-counter drugs available to the public. This law was the first to introduce a new assumption that bioequivalent drugs are therapeutically equivalent and therefore interchangeable. Approved Drug Products with Therapeutic Equivalence Evaluations, commonly referred to as the Orange Book, identifies FDA-approved drugs based on safety and efficacy. Regarding the status of the "Orange Book", it should be noted that informing about its assessment of the therapeutic equivalence of drugs using the list, the FDA offers its recommendations to the public, specialists and authorized bodies on the choice of a drug. Such an assessment should not be considered as a prohibition to use one or another drug, or as evidence that one of them is preferable to the other. For the most part, the Orange Book does not serve to distinguish multisource drugs among themselves, but informs about whether the available tools have succeeded in solving the problem of proving their therapeutic equivalence to a reference drug or not. Therapeutic equivalence is a scientific judgment, while generic substitution practices aimed at cost savings are also based on social and economic considerations.

The Orange Book is related to the fact that in order to save money in the health care system, virtually all US states have passed laws and / or regulations to encourage generic substitution. The implementation of these laws required the creation of a positive or negative list of drugs (those that either can or cannot replace the original drug). FDA specialists have created a single formulary of medicines, in which the

assessment of therapeutic equivalence of drugs was presented in the form of an alphabetic code. The system of letter codes describing therapeutic equivalence allows you to quickly determine whether the bioequivalence of a particular drug has been established with a reference (first letter), and to obtain additional information about the FDA assessment (second letter). The two main categories that generic drugs can be classified into are designated by the letters A and B. Category A includes drugs that are therapeutically equivalent to other pharmaceutically equivalent products for which:

• no known or suspected bioequivalence problems; they are designated by the letters AA, AN, AO, AP or AT, depending on the dosage form;

• actual or potential bioequivalence problems can be resolved by adequate evidence of bioequivalence; in such cases, the designation AB is used.

Code B refers to drugs that the FDA currently considers to be not therapeutically equivalent to other pharmaceutically equivalent products, i.e. actual or potential bioequivalence problems cannot be resolved by adequately establishing bioequivalence. Often the problem lies in the specific dosage form, not the active ingredient. In such cases, the designations BC, BD, BE, BN, BP, BR, BS, BT, BX or B are used.

At one time, the FDA published draft guidelines on the activities of pharmaceutical companies, as well as enterprises that were owned or influenced by distributors (so-called sponsors) of medical products. The need to hold public hearings and discuss the project was due to the fact that individuals and groups of people appealed to state legislatures, pharmaceutical organizations, as well as to drug control committees, expressing concern about the problem of interchangeability of certain drugs, in particular drugs with limited therapeutic index. They were especially interested in whether the safety and efficacy indicators of such drugs would change if, instead of a drug from a well-known manufacturer, they began to use a drug recognized by the FDA as therapeutically equivalent, but not protected by a registered trademark. A letter from FDA Health Commissioner Stuart L. Nightingale was published to clarify this topic in 1998. The following is his summary “Based on the determination of therapeutic equivalence of drugs, the FDA made a statement:

• additional clinical tests are not required when replacing a drug of a well-known company with a drug with an unregistered trademark;

• No special precautions need to be taken when changing the formula or manufacturing process of a drug, provided the changes are approved by the FDA in accordance with FDA laws and regulations;

• as stated in the Orange Book, the FDA believes that drugs that are found to be therapeutically equivalent will have the same clinical effect, regardless of whether the drug is known or new;

• There is no need to treat any drug class as distinct from another class if the FDA has determined therapeutic equivalence for the drugs in question. "

According to the FDA, drugs are considered therapeutically equivalent if they meet the following general requirements:

a) their effectiveness and safety have been proven;

b) they are pharmaceutically equivalent, namely:

• contain the same amount of identical active ingredients in the same dosage form and are intended for one route of administration;

• meet the requirements for strength of action, quality, purity and identity;

c) are bioequivalent, namely:

• there are no known or potential bioequivalence problems and they comply with the in vitro standard; or • if the existing known or potential problems can be eliminated by conducting bioequivalence studies;

d) adequate instructions in the instructions;

e) produced in accordance with GMP requirements.

According to the WHO definition, two drugs are considered therapeutically equivalent if they are pharmaceutically equivalent, have the same bioavailability of the drug and, after administration in the same molar dose, their action provides appropriate efficacy and safety.

Thus, therapeutic equivalence is the main requirement for drug interchangeability.

Finally, in some cases, special evidence of therapeutic equivalence is not required, for example, provided that all chemical (for example, impurity profile), pharmaceutical

(for example, stability) and manufacturing (GMP) indicators correspond to those of the selected standard. In other words, in these cases, the conformity of the technical parameters is considered to guarantee therapeutic equivalence in itself. In all cases, we are talking about comparative trials with drugs, the therapeutic efficacy of which is considered proven.

Based on the above, it is clear that therapeutic equivalence includes pharmaceutical equivalence and one of the criteria:

• study of bioequivalence in humans;

• research of pharmacodynamics in humans;

• clinical trials;

• in vitro dissolution test (in some cases).

Generic production and quality control are also dependent on excipients. The requirements for them should be the same as for the active substance. Any change in the composition of the fillers or the drug shell can significantly change the quality of the drug, its bioavailability, and lead to toxic or allergic phenomena.

The concept of therapeutic equivalence applies only to medicines containing the same active ingredients and does not apply to different therapeutic agents used in similar clinical situations (for example, paracetamol and acetylsalicylic acid prescribed for headache).

A medicinal product that meets the above criteria for therapeutic equivalence is considered as such, even if it differs in some characteristics, such as shape, risk per tablet, packaging, excipients (including dyes, preservatives), shelf life and minimal differences in the instructions (for example, the presence of a specific information on pharmacokinetics), as well as storage conditions. If such differences are important in the treatment of a particular patient, the doctor may require that a particular brand be released from the pharmacy. Apart from this limitation, the FDA believes that drugs classified as therapeutically equivalent can be substituted with full reliance on the substitution effect and safety profile expected from the prescribed drug.

It must be admitted that both in the EU countries and in the USA, many experts question pharmacokinetic equivalence as the only way to assess drug

interchangeability. A number of publications indicate significant methodological shortcomings in the study of bioequivalence of drugs, which may lead to the fact that the existing differences between branded and generic drugs will not be identified. According to European requirements and FDA regulations, individual pharmacokinetic parameters can differ by up to 20%. It is believed that fluctuations in the concentration of the active component in the blood plasma in the range from -20 to + 25% are clinically insignificant, however, for elderly patients or other vulnerable groups of patients, even such insignificant changes in the concentration of the drug may increase the risk of side effects.

It is assumed, for example, that certain restrictions may be associated with the existence of drugs characterized by a relatively small range of therapeutic drug concentrations in blood plasma (some antidepressants - paroxetine, fluoxetine, citalopram) and / or nonlinear pharmacokinetics (normotimics and antiepileptic drugs) [10].

In this situation, even small changes in this parameter, which are well within the acceptable limits of the bioequivalence test (from -20 to + 25%), may be significant for clinical efficacy and / or tolerability [14, 37].

Consequently, there may be significant discrepancies in the properties of branded and generic drugs. For example, with bioequivalence values below 100%, the drug may be ineffective. On the contrary, with an increase in the indicator under consideration, an increase in the number of side effects should be expected. Of particular concern are drugs with a low therapeutic index (the difference between the minimum effective dose of the drug and its maximum toxic dose) - digoxin, phenytoin, carbamazepine, cyclosporin, warfarin. This situation requires stricter and broader requirements for pharmacokinetic studies. The issue of reducing the differences in parameters to 10-15% is discussed, which will reduce the number of drugs with borderline pharmacokinetic parameters.

Another limitation is imposed on the use of bioequivalence test results by the existence of drugs (sertraline, fluoxetine, chlorpromazine, clozapine) with significant variability of pharmacokinetic parameters, which depends, in particular, on the complexity of drug metabolism (cytochrome system, the presence of several routes of excretion, etc. .).

Such variability can be "intraindividual" in nature. In one case, she is associated, for example, with the genetic polymorphism of cytochromes, which is observed in different populations of the population, in another - with the functional state of these enzymes, changing in the same person under the influence of various external factors (for example, the use of grapefruit juice). Consequently, the results of a bioequivalence test performed on a small group of volunteers who ate a similar diet may not be valid in a real clinical setting.

The tendency to use a single daily dose of drugs during bioequivalence studies is also critically perceived.

It is known that many drugs (amiodarone, digitalis drugs, psychotropic drugs) are prescribed multiple times over a certain period of time and to obtain a clinical effect, it is required to achieve a stable (therapeutic) concentration of the drug in blood plasma and / or tissue, which can be significantly higher than that used in bioequivalence studies in healthy volunteers.

It should also be borne in mind that in real clinical practice, generic drugs are taken for a long time by patients of different ages, sex, body weight, often suffering from comorbid (concomitant) pathology. In such a situation, the pharmacokinetic properties of branded and generic drugs, due to the existence of even small chemical differences between them, can differ significantly. The pathology of the gastrointestinal tract is acquiring a certain importance. In patients with this disease, a rather complex mechanism of drug absorption is easily disrupted. At the same time, even insignificant differences in the chemical composition of branded and generic drugs can lead to a violation of their bioequivalence.

In particular, a situation may arise when inert formulations (fillers) used in generics, when administered in a single dose, without affecting the absorption, distribution and metabolism of drugs, with prolonged use, can affect the functional state of the gastrointestinal tract, liver or kidney in such a way that the pharmacokinetic equivalence of drugs is significantly impaired.

As an example, we can cite various compositions of excipients of original and generic nicergoline preparations, widely used by patients of different ages, including elderly patients, often suffering from a wide range of concomitant diseases of internal organs. Another problem is associated with the presence of concomitant somatic pathology, which significantly complicates the clinical use of the results of the bioequivalence test. In contrast to healthy volunteers, patients with concomitant pathology are often forced to take various somatotropic drugs, in particular, enhancing or weakening peristalsis, affecting the destruction of the drug in the intestine. It is possible that this influence, due to the existing, albeit minimal, differences in the chemical composition of the original and generic drugs may turn out to be ambiguous. Accordingly, conditions arise for changing the bioequivalence of these drugs.

The objections discussed are not merely theoretical considerations. In the relevant publications, there is a lot of information about the results of cross-checking the bioequivalence of various drugs. These data indicate that a significant proportion of generics do not pass this test. So, conducted in the UK in 1995-1996. An analysis of 2,427 generic drugs found 228 significant differences. No less striking data were obtained in the United States. The FDA found that up to 20% of the brand and generic drugs available in the country are not bioequivalent and, therefore, cannot be interchangeable.

Examples of clinical nonequivalence of enalapril preparations are given. It was shown that the clinical efficacy of 4 generic enalapril from well-known manufacturers in achieving the target blood pressure level in patients with arterial hypertension was lower than that of the original drug (Renitek, MSD). The investigated generics were pharmacokinetically equivalent to Renitek. Based on the results obtained, the authors concluded that the reproduced drugs of enalapril were not the same therapeutic equivalence.

The therapeutic inequality of the original indapamide (Arifon, Servier) and its generics in patients with arterial hypertension was reported by V.I. Petrov et al., While the pharmacokinetic profiles of the compared drugs coincided.

The equivalence of generics is of particular importance for antimicrobial drugs, since low antimicrobial activity can lead to a decrease in the clinical effectiveness of therapy, which is especially important in the treatment of critically ill patients, and the rapid spread of resistant forms of microbes. A recent study of the mycological activity of original fluconazole (Diflucan, Pfizer) and generic drugs

The amount of solid particles in 4 generic cefotaxime preparations increased 10 times compared to the original drug (Claforan, Hoechst). These particles contained in generics can disrupt microcirculation in ischemic tissues and contribute to the development of respiratory distress syndrome and multiple organ failure in severe patients.

The literature provides a comparison of branded and generic clozapine (Clozaril, Novartis Pharmaceuticals and clozapine, Zenith Goldline Pharmeceuticals). In the course of the study, it was found that the discrepancy between these psychotropic drugs in terms of pharmacokinetic parameters is observed in 40% of patients with schizophrenia.

Significant differences in bioequivalence were revealed between branded drugs amitriptyline hydrochloride, nortriptyline hydrochloride, desipramine, trimipramine maleate and their generics.

More than 100 studies have been carried out on the bioequivalence of various generics of phenytoin and valproic acid preparations, in which significant discrepancies in the pharmacokinetic parameters of original and generic drugs were found.

Speaking of therapeutic equivalence, mention should be made of the study by R. Mofsen et al., Which describes 7 cases of unsuccessful replacement of branded clozapine with its generic drug in patients with a stable mental state who were in a neuropsychiatric institution. It is emphasized that this change in therapy was unexpectedly made by the pharmacy and neither the doctors nor the medical staff of the institution knew about it. It was a complete surprise for them that patients had resumed psychotic disorders, the severity of which in 5 out of 7 cases required urgent measures to transfer patients to a psychiatric hospital. A similar case has been reported when switching from branded paroxetine (Paxil) to its generic.

In a recent survey of neurologists (301 respondents) working in the United States, it was found that when switching from branded antiepileptic drugs to generic drugs, 204 (67.8%) of them observed a resumption of seizures, 168 (55.8%) noted an increase in side effects ...

There are 11 cases in which, after the replacement of branded lamotrigine with its generics, control over epileptic seizures was lost.

As a result of these studies, in a number of countries, including Norway, decisions have been made that limit the transfer of patients from branded antiepileptic drugs to generic drugs, and in Germany this procedure is generally not recommended.

A number of controlled studies have shown that when switching from branded carbamazepine to its generic drug, there is a sudden resumption of seizures.

Another paper, published in the American Journal of Cardiology in May 2000, cites the opinion of 64 expert electrophysiologists, members of the North American Society for the Stimulation of Electrophysiology, who report 32 cases of recurrent arrhythmias (ventricular fibrillation, ventricular tachycardia, atrial fibrillation and atrial tachycardia) in replacement of the branded antiarrhythmic drug amiodarone (Cordarone, Sanofi-Synthelabo) with its generics.

It should be noted that there are also publications on the therapeutic equivalence of original and generic drugs. One randomized, double-blind study examined two parallel groups of outpatients with chronic schizophrenia receiving branded fluphenazine decanoate. The first group was switched to its generic drug, the second was left to the original drug. After 12 weeks, there was no significant change in the condition in both groups, as determined by a special scale of positive and negative syndrome.

Speaking about chronic diseases, it should be noted that many of them tend to recur. In view of this, current recommendations provide for, along with stopping, long-term supportive therapy. In practice, a situation is often observed when the arresting therapy, which is carried out most often in a hospital, is carried out with an original drug. Later, after the patient is discharged, this drug is often replaced by its generic due to “economic” considerations. In the light of the data presented above, it is obvious that the considered replacement is possible only if there is confidence in the

pharmaceutical, pharmacokinetic and therapeutic equivalence of the original and reproduced drugs.

There are reports that the introduction of generic drugs on the pharmaceutical market does not always lead to a reduction in direct health care costs. A recent Canadian study analyzed that the 11% difference in relapse rates observed with generic versus original clozapine negated the generic cost advantage. Similar data were obtained for antiepileptic drugs. The given data, like many others, in the opinion of the chief clinical pharmacologist of the Ministry of Health of the Russian Federation, Professor Yu.B. Belousov, dispel the myth about the cheapness of generics, since the costs of using them are much higher than when using original drugs. Contrary to popular claims that generic drugs reduce direct treatment costs, promote competition and lower prices for branded drugs, and even represent one of the ways to introduce cost-effective medical technologies into clinical practice, some recent research suggests otherwise.

The scientist believes that the transition from inexpensive generics to original drugs is beneficial for both patients and society as a whole. He believes that it is unacceptable to transfer the data on efficacy and safety obtained on original drugs to their copies. Only the availability of complete information on compliance with GMP requirements in the production of a generic drug, its pharmacokinetic and therapeutic equivalence in comparison with the original drug, make it reasonable to search for the pharmacoeconomic advantages of a generic drug. Otherwise, formally favorable price indicators can result in huge additional costs, for example, in the treatment of unwanted side effects. According to Yu.B. Belousov, the practice that has developed in the Russian Federation, which permits the medical use of a generic based on data only of its bioequivalence, is incorrect. To determine therapeutic equivalence, it is necessary to conduct both limited and large clinical trials of the efficacy of a generic for a specific disease, to study the comparative efficacy of the original and generic drugs using clear end criteria. Therapeutic equivalence also means the organization of studies of the safety profile of generics with intensive monitoring within 5 years after the registration of unwanted effects.

It is obvious that original drugs will always be opposed to generic ones, but their competition in the pharmaceutical market should be based on strict adherence to quality requirements for the production of both original and generic drugs, on the results of bioequivalence analyzes, as well as data from clinical trials. Therefore, the widespread use of generic drugs in clinical practice should be based on clear instructions available to practitioners about their pharmaceutical, pharmacokinetic, and, above all, therapeutic equivalence to the original drugs.

### 1.4. Overview of the use of antacids in medicine

Antacids (alkaline anti-acid agents) are the most studied group of drugs today, which have a long history and have been used in medicine since ancient times. Even the ancient Romans treated "stomach diseases" with crushed coral, that is, calcium carbonate. In modern medicine, more than a hundred antacids are used, different in form, composition, strength of action, organoleptic properties, and price. The rapidity of the onset of the therapeutic effect (primarily the elimination of pain or heartburn) attracts the attention of doctors and patients to this group of medications, despite the fact that in recent decades, new powerful blockers of gastric secretion have appeared. However, if H2-blockers and proton pump inhibitors (PPIs), acting on various parts of the parietal cell of the stomach, suppress the production of hydrochloric acid, then antacids do not directly affect the functioning of the parietal cell and act on acid that has already been released into the lumen of the stomach. The mechanism of action of antacids consists of neutralizing free hydrochloric acid of gastric juice, preventing reverse diffusion of hydrogen ions, adsorption of pepsin and bile acids, in addition, cytoprotection, reducing pressure in the stomach and duodenum, counteracting muscle spasm and duodeno-gastric reflux, shortening the evacuation time of the gastric content.

Currently, a wide range of antacids is presented on the Russian pharmacological market, the main components of which are sodium bicarbonate, calcium carbonate, aluminum hydroxide and phosphate, citrate, carbonate, magnesium oxide and hydroxide. Currently used antacids differ in the speed of the onset of the effect, its

duration, as well as the ability to have a systemic effect and form carbon dioxide in the stomach. Antacids are classified as water-soluble and insoluble.

Sodium bicarbonate and calcium carbonate dissolve in water, act quickly, while forming carbon dioxide, which causes distension of the stomach and stimulates the secondary hypersecretion of hydrochloric acid (ricochet syndrome). Sodium bicarbonate, due to its solubility in water, is able to be absorbed and have a systemic effect; with prolonged and excessive use of this antacid, acidosis can develop.

Compounds of magnesium and aluminum do not dissolve in water, they differ in a slower onset of effect compared to sodium and calcium salts with longer exposure. In addition, the buffering capacity of magnesium and aluminum compounds is higher than that of sodium and calcium salts. These compounds are practically not absorbed into the bloodstream and partially absorb toxins. In large quantities, magnesium salts have a laxative effect, aluminum - locking.

Unlike absorbed antacids, prolonged use of nonabsorbable drugs does not lead to the development of the rebound phenomenon. The mechanism of this phenomenon may be due to the fact that nonabsorbable antacids not only neutralize hydrochloric acid, but also absorb pepsin, which leads to suppression of the biosynthesis of hydrochloric acid. The mechanism of action, characteristic of non-absorbable drugs, is slower than the binding of hydrochloric acid, but the effect persists for a longer time.

In recent years, complexes containing several compounds have been increasingly used as antacids. Thanks to this, it is possible to vary the rate of onset of the therapeutic effect, the duration of the drug's effect, and also to minimize its side effects. In addition, some modern drugs also have a gastroprotective effect due to the special additives they contain.

1.5. Dissolution test in quality control of medicines.

Solubility is the most important property of drugs intended for oral administration (parenteral) or absorption in the oral cavity (sublingual). This characteristic directly depends on whether the active substance can be released (go into solution) from a tablet, capsule, dragee, powder, granulate, candy, etc .:

• in a certain part of the gastrointestinal tract;

• at the required time;

• in the required quantity;

• at an appropriate speed.

Some other dosage forms also have solubility (hydrophilic suppositories, implants, patches with transdermal active substance transit, stents, etc.).

If the kinetics of dissolution corresponds to the norm for a particular drug, one can count on the expected therapeutic effect and the absence of unwanted side effects.

That is why the determination of solubility is included in the mandatory list of methods used to assess the quality of drugs in the process of their development, manufacture and examination.

The solubility of tablets and other solid dosage forms is assessed according to the methods defined by the world's leading Pharmacopoeias and the WHO International Pharmacopoeia. For dissolution testing, specialized equipment is used - testers with different operating principles, functionality and performance.

Currently, the share of registered generics in the Russian pharmaceutical market is more than 80%, therefore, the issues of quality control are an urgent problem. The quality of drugs, as well as their interchangeability, can be assessed using the "Dissolution" test, designed to assess the degree of release of an active substance from solid dosage forms, which include tablets and capsules.

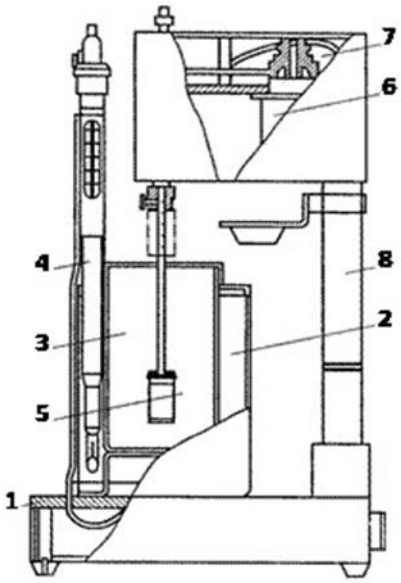
Solid dosage forms have many advantages: ease of use, dosing accuracy, the ability to localize the action of a drug in a specific part of the gastrointestinal tract. Their effectiveness also depends on the rate of dissolution of the medicinal substance. The "Dissolution" test allows you to determine how quickly the drug will dissolve in the body, and theoretically assume after what time its therapeutic effect will begin to manifest itself. Test conditions are closest to physiological parameters. The "Dissolution" test is carried out on the "Rotating Basket", "Paddle Stirrer" and "Flow Cell" devices, the number of revolutions of the blade or basket, as well as the flow rate, are selected during the experiment. As a dissolution medium, solutions are used, the pH values of which correspond to the pH values in different parts of the gastrointestinal tract. If the release of a drug from a tablet or capsule is to take place in the stomach,

then this drug will dissolve well in a buffer solution with a low pH value. However, the medicinal substances that make up the drug have different physicochemical properties, therefore, for each drug (MP), a dissolution medium is selected, taking into account its chemical structure and the composition of excipients. As a dissolution medium, you can use artificial gastric and intestinal juice without the addition of enzymes. The volume of the dissolution medium corresponds to the volume of the stomach contents on an empty stomach plus a glass of water. Usually tablets or capsules are dissolved in 500 ml of buffer solution, but the volume can be increased up to 900 ml. The temperature of the dissolution medium should be the same throughout the experiment and correspond to the temperature of the body fluid - 37 ° C. Sampling is carried out at regular intervals depending on the duration of the drug's action. So, for dosage forms of immediate release, the dissolution time is 45 minutes, and for tablets or capsules of prolonged action, the test is carried out within 24 hours.

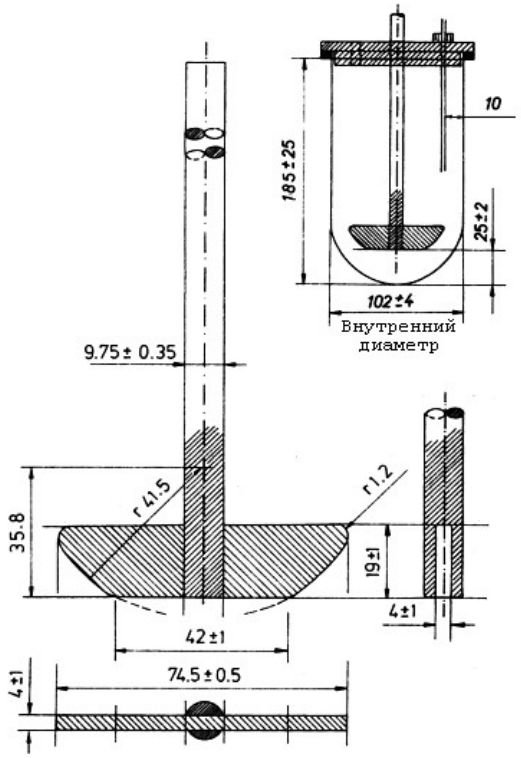
At the same time, the “Dissolution” test is an effective tool for establishing the interchangeability of original and generic drugs. Consider an example of this test to assess the equivalence of drugs containing one of the most common non-steroidal anti-inflammatory substances. The results of the experiment are displayed graphically in the form of dissolution profiles. Figure 1 shows the dissolution profiles of the original drug and its generic in a pH 1.2 buffer solution, and Figure 2 - in a 4.5 buffer solution. If you look at the given graphs, they are outwardly similar, however, it is still impossible to make a reliable conclusion about the similarity. Evaluation of the equivalence of dissolution profiles is carried out on the basis of statistical processing by calculating the convergence factor, the values of which must fit into a certain interval.

After carrying out the necessary calculations, it was concluded that the dissolution profiles for the original and generic drug are equivalent only when the experiment is carried out in a buffer solution of pH 4.5. The similarity of the profiles of these drugs makes it possible to assess their therapeutic equivalence, i.e. talk about their interchangeability in clinical practice.

USP Dissolution Methods According to the requirements of the American Pharmacopoeia (USP), dissolution of tablets of various types, capsules and other dosage forms is carried out according to the following standardized methods:




Rotating Basket (USP1). This analysis requires a special type of rotating element - a basket, which allows the sample to be retained in the dissolution medium. The method is used to test capsules and other samples that tend to float to the surface. Not suitable for dissolution testing of disintegrating tablets: the resulting flakes can clog the cells of the basket, as a result of which the reliability of the test results is reduced.

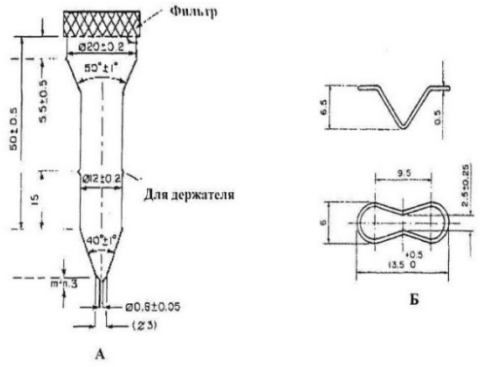



Paddle stirrer (USP2). The most common method for testing solubility. The dissolution test is carried out inside a vessel of a certain geometry and volume. The sample is placed directly into the medium, which is stirred during the experiment with the blades of the stirrers. The method provides highly reliable results in the analysis of almost all types of solid dosage forms, with the exception of hard-to-dissolve tablets. In particular, it can be used to study light floating samples that are supplied with special weights.

Oscillating Cylinder (USP3). The technique is in demand in the research sector when simulating the natural conditions of transit through the gastrointestinal tract of new drugs. Use in routine analysis is limited.

Blade Over Disc (USP5). A highly specialized method for assessing the solubility of transdermal and sublingual pharmaceuticals.

Rotating Cylinder (USP6). The technique is recommended for testing the dissolution kinetics of some transdermal for.




Flow Cell (USP4). In flow cells, a dissolution test is carried out for prolonged (slowly dissolving) and sparingly dissolving drugs.

**Swing Holder (USP6). Oscillating holders are used to analyze the solubility of eye implants, transdermal preparations, difficult-to-dissolve tablets (prolonged release).**

**Analytical equipment Pharma Test for determination of solubility: features and benefits.**

Modern high-tech analyzers developed by Pharma Test in strict accordance with pharmacopoeial requirements allow the dissolution kinetics test according to the USP2, USP1, USP5 and USP6 methods.

The PTWS series tablet dissolution testers with manual sample preparation are represented by a line of devices that differ:

• the number of testing stations (from base 6 to 12);

• the number of electric drives (from 1 to 6);

• volumes of vessels (from 250 ml to 4 liters);

• other design and technological features.

The analyzers are equipped with:

• remote thermostating units with independent temperature sensors, automatic protection against overheating and flow sensors (modular design allows you to completely eliminate vibration of testing stations during dissolution testing).

• the unique MonoShaftTM system for quick and easy change of rotating elements;

• built-in memory for simultaneous storage of up to 100 different methods;

• removable plexiglass water bath;

• electronic lifts for lowering / raising the control unit with stirring devices;

• ports for communication with spectrophotometers and other external modules (optional).

**Basic analyzer with optimized functionality and compact size. Ideally suited for the vast majority of routine examinations**

**1.4 Automobiles were initially developed as self-propelled versions of horse-drawn vehicles.**

However, horse-drawn vehicles had been designed for relatively slow speeds, and their suspension was not well suited to the higher speeds permitted by the internal combustion engine.

The first workable spring-suspension required advanced metallurgical knowledge and skill, and only became possible with the advent of industrilisation. Obadiah Elliott registered the first patent for a spring-suspension vehicle; each wheel had two durable steel leaf springs on each side and the body of the carriage was fixed directly to the springs which were attached to the axles. Within a decade, most British horse carriages were equipped with springs; wooden springs in the case of light one-horse vehicles to avoid taxation, and steel springs in larger vehicles. These were often made of low-carbon steel and usually took the form of multiple layer leaf springs.[4]

Leaf springs have been around since the early Egyptians. Ancient military engineers used leaf springs in the form of bows to power their siege engines, with little success at first. The use of leaf springs in catapults was later refined and made to work years

later. Springs were not only made of metal; a sturdy tree branch could be used as a spring, such as with a bow. Horse-drawn carriages and Ford Model T used this system, and it is still used today in larger vehicles, mainly mounted in the rear suspension.

Any four-wheel-drive (4WD/AWD) vehicle needs suspension for both the front wheels and rear wheels, but in two-wheel-drive vehicles there could be a very different configuration.

For front-wheel drive cars, rear suspension has few constraints, and a variety of beam axles and independent suspensions are used. For rear-wheel drive cars, rear suspension has many constraints, and the development of the superior, but more expensive independent suspension layout has been difficult. Four-wheel drive often has suspensions that are similar for both the front and rear wheels.

Spring rate

The spring rate (or suspension rate) is a component in setting the vehicle's ride height or its location in the suspension stroke. When a spring is compressed or stretched, the force it exerts, is proportional to its change in length. The *spring rate* or *spring constant* of a spring is the change in the force it exerts, divided by the change in deflection of the spring. Vehicles that carry heavy loads, will often have heavier springs to compensate for the additional weight that would otherwise collapse a vehicle to the bottom of its travel (stroke). Heavier springs are also used in performance applications, where the loading conditions experienced are more significant.

Springs that are too hard or too soft cause the suspension to become ineffective – mostly because they fail to properly isolate the vehicle from the road. Vehicles that commonly experience suspension loads heavier than normal, have heavy or hard springs, with a spring rate close to the upper limit for that vehicle's weight. This allows the vehicle to perform properly under a heavy load, when control is limited by the inertia of the load. Riding in an empty truck meant for carrying loads can be uncomfortable for passengers, because of its high spring rate relative to the weight of the vehicle. A race car could also be described as having heavy springs, and would also be uncomfortably bumpy. However, even though we say they both have heavy springs,

the actual spring rates for a 2,000 lb (910 kg) racecar and a 10,000 lb (4,500 kg) truck are very different. A luxury car, taxi, or passenger bus would be described as having soft springs, for the comfort of their passengers or driver. Vehicles with worn-out or damaged springs ride lower to the ground, which reduces the overall amount of compression available to the suspension, and increases the amount of body lean. Performance vehicles can sometimes have spring rate requirements other than vehicle weight and load.

Wheel rate is the effective spring rate when measured at the wheel, as opposed to simply measuring the spring rate alone.

Wheel rate is usually equal to or considerably less than the spring rate. Commonly, springs are mounted on control arms, swing arms or some other pivoting suspension member. Consider the example above, where the spring rate was calculated to be 500 lbs/inch (87.5 N/mm), if one were to move the wheel 1 in (2.5 cm) (without moving the car), the spring more than likely compresses a smaller amount. If the spring moved 0.75 in (19 mm), the lever arm ratio would be 0.75:1. The wheel rate is calculated by taking the square of the ratio (0.5625) times the spring rate, thus obtaining 281.25 lbs/inch (49.25 N/mm). Squaring the ratio is, because the ratio has two effects on the wheel rate: the ratio applies to both the force and the distance traveled.

Wheel rate on independent suspension is fairly straightforward. However, special consideration must be taken with some non-independent suspension designs. Take the case of the straight axle. When viewed from the front or rear, the wheel rate can be measured by the means above. Yet, because the wheels are not independent, when viewed from the side under acceleration or braking, the pivot point is at infinity (because both wheels have moved) and the spring is directly inline with the wheel contact patch. The result is often, that the effective wheel rate under cornering is different from what it is under acceleration and braking. This variation in wheel rate may be minimised by locating the spring as close to the wheel as possible.

Wheel rates are usually summed and compared with the sprung mass of a vehicle to create a "ride rate" and the corresponding suspension natural frequency in ride (also

referred to as "heave"). This can be useful in creating a metric for suspension stiffness and travel requirements for a vehicle/

**Damping**

Damping is the control of motion or oscillation, as seen with the use of hydraulic gates and valves in a vehicle's shock absorber. This may also vary, intentionally or unintentionally. Like spring rate, the optimal damping for comfort may be less, than for control.

Damping controls the travel speed and resistance of the vehicle's suspension. An undamped car will oscillate up and down. With proper damping levels, the car will settle back to a normal state in a minimal amount of time. Most damping in modern vehicles can be controlled by increasing or decreasing the resistance to fluid flow in the shock absorber.

**Camber control**

See dependent and independent below. Camber changes due to wheel travel, body roll and suspension system deflection or compliance. In general, a tire wears and brakes best at -1 to -2° of camber from vertical. Depending on the tire and the road surface, it may hold the road best at a slightly different angle. Small changes in camber, front and rear, can be used to tune handling. Some racecars are tuned with -2 to -7° camber, depending on the type of handling desired, and tire construction. Often, too much camber will result in the decrease of braking performance due to a reduced contact patch size through excessive camber variation in suspension geometry. The amount of camber change in bump is determined by the instantaneous front view swing arm (FVSA) length of suspension geometry, or in other words, the tendency of the tire to camber inward when compressed in bump.

**Roll center height**

Roll center height is a product of suspension instant center heights and is a useful metric in analyzing weight transfer effects, body roll and front to rear roll stiffness distribution. Conventionally, roll stiffness distribution is tuned adjusting antiroll

bars rather than roll center height (as both tend to have a similar effect on the sprung mass), but the height of the roll center is significant when considering the amount of jacking forces experienced.

Flexibility and vibration modes of suspension elements

In some modern cars, flexibility is mainly in rubber bushings, which are subject to decay over time. For high-stress suspensions, such as off-road vehicles, polyurethane bushings are available, which offer more longevity under greater stresses. However, due to weight and cost considerations, structures are not made more rigid than necessary. Some vehicles exhibit detrimental vibrations involving the flexing of structural parts, such as when accelerating while turning sharply. Flexibility of structures, such as frames and suspension links, can also contribute to springing, especially to damping out high-frequency vibrations. The flexibility of wire wheels contributed to their popularity in times when cars had less advanced suspensions.

**Load levelling**

Automobiles can be heavily laden with luggage, passengers, and trailers. This loading will cause a vehicle's tail to sink downwards. Maintaining a steady chassis level is essential to achieving the proper handling that the vehicle was designed for. Oncoming drivers can be blinded by the headlight beam. Self-levelling suspension counteracts this by inflating cylinders in the suspension to lift the chassis higher.

**Air resistance (drag)**

Certain modern vehicles have height adjustable suspension in order to improve aerodynamics and fuel efficiency. Modern formula cars that have exposed wheels and suspension typically use streamlined tubing rather than simple round tubing for their suspension arms to reduce aerodynamic drag. Also typical is the use of rocker-arm, push rod, or pull rod-type suspensions, that, among other things, place the spring/damper unit inboard and out of the air stream to further reduce air resistance.

**1.5 Semi-active and active suspensions**

If suspension is externally controlled, then it is a semi-active or active suspension — the suspension is reacting to signals from an electronic controller.

For example, a hydropneumatic Citroën will "know" how far off the ground the car is supposed to be, and constantly resets to achieve that level, regardless of load. However, this type of suspension will *not* instantly compensate for body roll due to cornering. Citroën's system adds about 1% to the cost of the car versus passive steel springs.

Semi-active suspensions include devices, such as air springs and switchable shock absorbers, various self-levelling solutions, as well as systems, like hydropneumatic, hydrolastic, and hydragas suspensions.

Toyota introduced switchable shock absorbers in the 1983 Soarer. Delphi currently sells shock absorbers filled with a magneto-rheological fluid, whose viscosity can be changed electromagnetically — thereby giving variable control without switching valves, which is faster and thus more effective.

Fully active suspension systems use electronic monitoring of vehicle conditions, coupled with the means to change the behavior of vehicle suspension in real time to directly control the motion of the car.

Lotus Cars developed several prototypes from 1982 onwards, and introduced them to Formula One, where they have been fairly effective, but have now been banned.

Nissan introduced low-bandwidth active suspension *circa* 1990 as an option that added an extra 20% to the price of luxury models. Citroën has also developed several active suspension models (see hydractive). A fully active system from Bose Corporation, announced in 2009, uses linear electric motors in place of hydraulic or pneumatic actuators that have generally been used up until recently. Mercedes introduced an active suspension system called Active Body Control in its top-of-the-line Mercedes-Benz CL-Class in 1999.

Several electromagnetic suspensions have also been developed for vehicles. Examples include the electromagnetic suspension of Bose, and the electromagnetic suspension developed by prof. Laurentiu Encica. In addition, the new Michelin wheel with embedded suspension functioning on an electric motor is also similar[23].

With the help of a control system, various semi-active/active suspensions realize an improved design compromise among different vibration modes of the vehicle; namely:

bounce, roll, pitch and warp modes. However, the applications of these advanced suspensions are constrained by cost, packaging, weight, reliability, and/or other challenges.

**Interconnected suspensions [edit]**

Interconnected suspension, unlike semi-active/active suspensions, could easily decouple different vehicle vibration modes in a passive manner. Interconnections can be realized by various means, such as mechanical, hydraulic, and pneumatic. Anti-roll bars are one of the typical examples of mechanical interconnections, while it has been stated, that fluidic interconnections offer greater potential and flexibility in improving both the stiffness and damping properties.

Considering the considerable commercial potentials of hydro-pneumatic technology (Corolla, 1996), interconnected hydropneumatic suspensions have also been explored in some recent studies, and their potential benefits in enhancing vehicle ride and handling have been demonstrated. The control system can also be used for further improving performance of interconnected suspensions. Apart from academic research, an Australian company Kinetic[24] had some success with various passive or semi-active systems (WRC: three Championships; the Dakar Rally: two Championships; Lexus GX470 2004 as the 4×4 of the year with KDSS; the 2005 PACE award). These systems by Kinetic generally decouple at least two vehicle modes (roll, warp (articulation), pitch, and/or heave (bounce)) to simultaneously control each mode's stiffness and damping by using interconnected shock absorbers, and other methods. In 1999, Kinetic was bought out by Tenneco. Later developments by the Catalan company Creuat have devised a simpler system design based on single-acting cylinders. After some projects on competition, Creuat is active in providing retrofit systems for some vehicle models.

Historically, the first mass-production car with front-to-rear mechanical interconnected suspension was the 1948 Citroën 2CV. Suspension in the 2CV was extremely soft — the longitudinal link was making pitch softer, instead of making roll stiffer. It relied on extreme anti-dive and anti-squat geometries to compensate for that. This resulted in a

softer axle-crossing stiffness that anti-roll bars would have otherwise compromised. The leading arm / trailing arm swinging arm, fore-aft linked suspension system, together with in-board front brakes, had a much smaller unsprung weight than existing coil spring or leaf designs. The interconnection transmitted some of the force deflecting a front wheel up over a bump, to push the rear wheel down on the same side. When the rear wheel met that bump a moment later, it did the same in reverse, keeping the car level front to rear. The 2CV had a design brief to be able to be driven at speed over a ploughed field, such as by a farmer transporting chicken eggs. It originally featured friction dampers and tuned mass dampers. Later models had tuned mass dampers at the front with telescopic dampers/shock absorbers front and rear.

**Dependent suspensions**

Dependent systems may be differentiated by the system of linkages used to locate them, both longitudinally and transversely. Often, both functions are combined in a set of linkages.

Examples of location linkages include:

- Satchell link
- Panhard rod
- Watt's linkage
- WOBLink
- Mumford linkage
- Leaf springs used for location (transverse or longitudinal)
    - Fully elliptical springs usually need supplementary location links, and are no longer in common use
    - Longitudinal semi-elliptical springs used to be common, and are still used in heavy-duty trucks and aircraft. They have the advantage, that the spring rate can easily be made progressive (non-linear).
    - A single transverse leaf spring for both front wheels and/or both back wheels, supporting solid axles, was used by Ford Motor Company, before and soon.

after World War II, even on expensive models. It had the advantages of simplicity and low unsprung weight (compared to other solid-axle designs).

In a front-engine rear-drive vehicle, dependent rear suspension is either "live-axle" or deDion axle, depending on whether or not differential is carried on the axle. Live-axle is simpler, but unsprung weight contributes to wheel bounce.

Because it assures constant camber, dependent (and semi-independent) suspension is most common on vehicles that need to carry large loads as a proportion of the vehicle's weight, that have relatively soft springs and that do not (for cost and simplicity reasons) use active suspensions. The use of dependent front suspension has become limited to heavier commercial vehicles.

**Independent suspensions**

The variety of independent systems is greater, and includes:

- Swing axle
- Sliding pillar
- MacPherson strut/Chapman strut
- Upper and lower A-arm (double wishbone)
- Multi-link suspension
- Semi-trailing arm suspension
- Swinging arm
    - Transverse leaf springs when used as a suspension link, or four-quarter elliptics on one end of a car are similar to wishbones in geometry, but are more compliant. Examples are the front of the original Fiat 500, then Panhard Dyna Z, and the early examples of Peugeot 403, and the backs of AC Ace and AC Aceca.
- Because the wheels are not constrained to remain perpendicular to a flat road surface in turning, braking, and varying load conditions, control of the wheel camber is an important issue. Swinging-arm was common in small cars that were sprung softly, and could carry large loads, because the camber is independent of

load. Some active and semi-active suspensions maintain ride height, and therefore the camber, independent of load. Sport cars, optimal camber change when turning, is more important.

- Wishbone and multi-link allow the engineer more control over the geometry, to arrive at the best compromise, than swing axle, MacPherson strut, or swinging arm do; however, the cost and space requirements may be greater.
- Semi-trailing arm is in between, being a variable compromise between the geometries of swinging arm and swing axle.

## CHAPTER II. METHODS AND OBJECTS

### 2.1. Research methods and objects, initial substances.

Suspension "Almidosis".

**Content:**

Magnesium hydroxide (gel form) 600 mg;

Aluminum hydroxide (gel form) 525 mg.

Analysis methods: "Authenticity", "Quantitative Analysis" ,.

**Reagents:**

Hydrochloric acid (diluted), sodium edetate, acetate buffer, dithizone solution in ethanol, zinc sulfate, ammonia buffer, black chrome indicator, Trilon B solution, magnesium sulfate, ammonium chloride, ammonia, sodium phosphate, barium chloride, ammonium oxalate, acetic acid , nitric acid (diluted), silver nitrate, dark blue chromated indicator.

Instruments:

Glass flask 250 ml,

Cylinder 25 ml,

Cylinder 10 ml,

Glass flask 50 ml,

Pipette,

Pipes,

Burette,

10 ml conical flask,

Scales.

Determination of the particle size in the Almidoz suspension was carried out using optical microscopy.

An optical microscope examines invisible drug samples and examines particles.

The particle size that can be checked by this method is determined by the size of the microscope and is usually 1 micron or more. However, if necessary, microscopes with a total magnification of more than 1500 can be used, which makes it possible to describe individual structures of objects larger than 0.5 μm with a resolution of up to 0.1 μm.

Pharmacopoeial analysis is used in optical microscopy to determine particle size during quality control of soft dosage forms, suspensions, emulsions, aerosols; in the technology of dosage forms - to determine the degree of grinding of substances and excipients, as well as to study crystalline substances, the shape, color and size of crystals are the individual properties of a substance.

**Equipment**

Typically, an optical microscope has a two-stage magnification system formed by the lens and the eye.

All microscope assemblies are mounted on a large base. On this base, a tube holder is installed, in which the lens and eyecup are fixed. Under the objective is a stage with an illumination system (mirror, collector, condenser). To illuminate the object of observation, you can use natural light and special light sources (indoor or outdoor lamps).

The microscope can be equipped with accessories (phase-contrast devices, dark capacitors, polarizers, analyzers, etc.) and, depending on the chosen observation method, it can be light, dark, phase-contrast, polarization, etc.

Light from the light source passes through the lighting system and the object and enters the mirror or recording system installed in its place, into a photo or video camera. This is done by visual inspection of the object, and a digital photo or video camera connected to a computer allows you to record images of the object, after which they can be processed by special programs in a semi-automatic or fully automatic mode.

The magnification of the microscope (for the manufacture of lenses, spectacles and additional consoles) should be sufficient to adequately describe and identify the smallest particles of the sample.

The maximum digital aperture of the lens should be selected for each zoom range. We recommend using color filters with a relatively narrow bandwidth to control the contrast and detail of colored objects. Color filters can also be used for achromatic (colorless) objects.

Adjustment, centering and calibration of all elements of the optical system are performed according to the instructions attached to the microscope.

Cooking samples

Test pieces can be tested both unused and liquid. The nature of the used immersion liquid is largely determined by the physical properties of the sample, which should not dissolve in it. Unless otherwise noted, mineral oil is used as a liquid in the research of pharmaceuticals and excipients.

Dust particles must be in the same plane and spread, forming separate particles (particle stickiness is unacceptable).

In addition, when preparing the sample for the microscope (including dispersion in liquid), it is necessary to maintain the original particle size and distribution in accordance with the sample size.

As mentioned in the Pharmacopoeia article, dosage forms are analyzed without formation or dilution.

When examining 5-10mg of powder, stop at 10ml of liquid and add moisturizer as needed. 1-2 drops of a homogeneous suspension containing at least 10 mg of the substance are placed on the objective glass in the counting zone of the microscope.

For each substance, the size and the permissible amount of particles exceeding this limit are determined for the purposes of the research specified or carried out in the monograph.

The analysis of dosage forms (in terms of "particle size") is carried out as described in the corresponding monograph.

Particle shape:

1.equilateral: particles of the same length, width and thickness, including cubic and spherical particles;

2.Needle: fine needle-like particles or similar

4. Maximum horizontal size;

5. The maximum volume of a particle, directed parallel to the scale of the length of the eye, from one end to the other;

6. Width is the maximum particle size and length is measured at right angles.

A single particle usually means the smallest formation. The particles can be liquid or viscous droplets, mono- or polycrystalline, amorphous or agglomerate.

By the degree of particle organization:

- plate boring plates;
- aggregates - the mass of particles sticking to each other;
- agglomerates - alloys or synthesized particles;
- conglomerates - a mixture of two or more types of particles;
- spherical cluster of spherulites-thin needle crystals;
- drusen - particles covered with very small particles.

Particle surface:

- soft asymmetries;
- rough-uneven, not smooth;
- fragile - partially separated, destroyed, with cracks;
- there are pits or walks;
- open - with small honeycombs.

Particle Description:

- by the shape of the edges - angular, twisted, smooth, sharp, brittle;
- by optical properties - colored, transparent, translucent, transparent;
- by the presence of defects - including interspersed.

Particle size

Determination of the particle size of the suspension is carried out using an optical microscope (OFS "optical microscope") and laser diffraction (OFS "determination of the particle size distribution using laser light diffraction").

Particle size is determined using the following method using an optical microscope.
A certain amount of suspension, corresponding to 10 μg of solid drug, is introduced into a counting chamber or applied to a vial using a micropipette and the entire sample area is examined under a microscope. Initially, the sample can be viewed in a small size (eg 50 ×), which defines particles larger than 25 microns. These particles are then measured on a large scale (eg, 200x to 500x). Maximum particle size is not allowed. 100 microns, unless otherwise indicated in the monograph or regulatory documents.
For a suspension of the ophthalmic type with a solid drug of 10 μg, there should be no more than 25 particles with a maximum size of more than 20 microns - no more than 50 particles with a maximum size of more than 2 microns, no more than 90 microns, the maximum size is not allowed.
2.2. The degree of opalescence may also be determined by instrumental measurement of the light absorbed or scattered on account of submicroscopic optical density inhomogeneities of opalescent solutions and suspensions. In practice, 2 techniques are used: nephelometry and turbidimetry. For turbidity measurement of coloured samples, ratio turbidimetry and nephelometry with ratio selection are used. The light scattering effect of suspended particles can be measured by observation of either the transmitted light (turbidimetry) or the scattered light (nephelometry). Ratio turbidimetry combines the principles of both nephelometry and turbidimetry. Turbidimetry and nephelometry are useful for the measurement of slightly opalescent suspensions. Reference suspensions produced under well-defined conditions must be used. For quantitation, the construction of calibration curves is essential, since the relationship between the optical properties of the suspension and the concentration of the dispersed phase is at best semi-empirical. The determination of opalescence of coloured liquids is done with ratio turbidimeters or nephelometers with ratio selection, since colour provides a negative interference, attenuating both incident and scattered light and lowering the turbidity value. The effect is so great for even moderately coloured samples that conventional nephelometers cannot be used. The instrumental assessment of clarity and opalescence provides a more discriminatory test that does not depend on the visual acuity of the analyst. Numerical results are more useful for quality monitoring and

process control, especially in stability studies. For example, previous numerical data on stability can be projected to determine whether a given batch of dosage formulation or active pharmaceutical ingredient will exceed shelflife limits prior to the expiry date.

**NEPHELOMETRY**

When a suspension is viewed at right angles to the direction of the incident light, the system appears opalescent due to the reflection of light from the particles of the suspension (Tyndall effect). A certain portion of the light beam entering a turbid liquid is transmitted, another portion is absorbed and the remaining portion is scattered by the suspended particles. If the measurement is made at 90° to the light beam, the light scattered by the suspended particles can be used for the determination of their concentration, provided the number and size of particles influencing the scattering remain constant. The reference suspension must maintain a constant degree of turbidity and the sample and reference suspensions must be prepared under identical conditions. The Tyndall effect depends upon both the number of particles and their size. Nephelometric measurements are more reliable in low turbidity ranges, where there is a linear relationship between nephelometric turbidity unit (NTU) values and relative detector signals. As the degree of turbidity increases, not all the particles are exposed to the incident light and the scattered radiation of other particles is hindered on its way to the detector. The maximum nephelometric values at which reliable measurements can be made lie in the range of 1750- 2000 NTU. Linearity between turbidity and concentration must be established by constructing a calibration curve using at least four concentrations. TURBIDIMETRY The optical property expressed as turbidity is the interaction between light and suspended particles in liquid. This is an expression of the optical property that causes light to be scattered and absorbed rather than transmitted in a straight line through the sample. The quantity of solid material in suspension can be determined by the measurement of the transmitted light. A linear relationship between turbidity and concentration is obtained when the particle sizes are uniform and homogeneous in the suspension. This is true only in very dilute suspensions containing

small particles. Linearity between turbidity and concentration must be established by constructing a calibration curve using at least four concentrations.

RATIO TURBIDIMETRY In ratio turbidimetry the relationship of the transmission measurement to the 90° scattered light measurement is determined. This procedure compensates for the light that is diminished by the colour of the sample. The influence of the colour of the sample may also be eliminated by using an infrared light-emitting diode (IR LED) at 860 nm as the light source of the instrument. The instrument's photodiode detectors receive and measure scattered light at a 90° angle from the sample as well as measuring the forward scatter (light reflected) in front of the sample along with the measurement of light transmitted directly through the sample. The measuring results are given in NTU (ratio) and are obtained by calculating the ratio of the 90° angle scattered light measured to the sum of the components of forward scattered and transmitted light values. In ratio turbidimetry, the influence of stray light becomes negligible. Nephelometers are used for measurements of the degree of opalescence of colorless liquids. Measurements of reference suspensions I - IV with a ratio turbidimeter show a linear relationship between the concentrations and measured NTU values (see Table 2.1.2.1.-2). Reference suspensions I - IV may be used as calibrators for the instrument. Table 2.1.2.1.-2. – Opalescent values for various formazin suspensions Formazin suspension

Opalescent value (NTU)

Reference suspension I 3

Reference suspension II 6

Reference suspension III 18

Reference suspension IV 30

Standard of opalescence 60

Primary opalescent suspension 4000.

INSTRUMENTAL DETERMINATION OF OPALESCENCE Requirements in monographs are expressed in terms of the visual examination method with the defined reference suspensions. Instrumental methods may also be used for determining compliance with monograph requirements once the suitability of the instrument as

described below has been established and calibration with reference suspensions I - IV and with water R or the solvent used has been performed. Apparatus. Ratio turbidimeters or nephelometers with selectable ratio application use as light source a tungsten lamp with spectral sensitivity at about 550 nm operating at a filament colour temperature of 2700 K, or infrared LED having an emission maximum at 860 nm with a 60 nm spectral bandwidth. Other suitable light sources may also be used. Silicon photodiodes and photomultipliers are commonly used as detectors and record changes in light scattered or transmitted by the sample. The light scattered at 90 ± 2.5° is detected by the primary detector. Other detectors are those to detect back and forward scatter as well as transmitted light. The instruments used are calibrated against standards of known turbidity; besides, instruments should be capable of automatic determination of turbidity. The test results expressed in NTU units are obtained directly from the instrument and compared to the specifications in the individual monographs. Instruments complying with the following specifications are suitable. - Measuring units: NTU. NTU is based on the turbidity of a primary reference standard of formazin. Total-metal determination In view of these considerations, it is advisable to study digestion procedures for heavy metals in sediments, from different origins. Selection of an extraction method on the basis of a minimal difference from the HF-method is one of the possibilities. Another possibility is to make a differentiation on the basis of the extent of destruction of metalliferous minerals in sediments. Such an evaluation of an extraction method, however, involves an intensive mineralogical analysis of the sediment before and after the extraction procedure. According to our present knowledge, the best extraction technique, for estimating the total contents of metals in sediments, is digestion by HF in combination with strong acids. Where the use of HF is considered objectionable, from a laboratorytechnical point of view, aqua regia is a reasonable alternative. The chemical analysis of a sediment usually consists of a digestion procedure and a determination of the extracted metals. To estimate the total metal contents of sediments, a rigorous digestion with strong acids, or combinations of strong acids, is generally used. Sediment analyses may be carried out, also, by other reliable methods such as X-ray fluorescence, neutron activation analysis and emission

spectrographic techniques. Digestion procedures, prior to an estimation of total amounts of metals in sediments, involve the use of HF, in most cases in combination with strong acids, e.g. aqua regia. However, in many laboratories HF is considered objectionable. Although using a teflon-bomb for the digestion procedure somewhat diminishes the disadvantage of the use of HF, the method remains rather laborious. Partly for this reason other methods, involving strong acids, are used in many laboratories. Although it is not yet known to what extent HF can be replaced by other digestion techniques, it is well known that different, 'strong attack' leaching procedures do not always dissolve equal amounts of metals. Diversity, both in sediments and in digestion procedures, gives rise to different amounts of extracted metals. In this connection, diversity in sediments refers to differences in the relative abundances of heavy metals in the crystal lattices of the individual minerals. Diversity in digestion procedures refers to their greater or lesser capability for destroying metalliferous minerals in the sediment. Grain size and metal concentration in sediments Although naturally metal-rich heavy minerals occur in the fine sand fractions, the highest concentrations of both natural and contaminant metals are usually found in the very fine grained muddy sediments. This non-uniform distribution of trace metals over the range of grain size fractions causes variations in the metal contents of sediment samples, even from within the same area. To compare the metal concentrations in sediments from different areas, and to determine the course of heavy metal pollution in time, corrections have to be made for differences in grain size composition. Different methods have been compiled by De Groot, Salomons & Allersma (1976), Förstner & Wittmann (1979) and Förstner & Salomons (1980). A summary is given below: A. Separation of grain size fractions 204 jum :— 175 jum 63 ßm B. C. 2 |Um; Extrapolation from regression curves % < 16 Mm % < 20 Mm - < 63 Mm specific surface area; Comparison with 'conservative' elements Ratio element/ aluminum. The generally linear relationship between metal contents and a grain size fraction (B), may be used as a suitable basis for the standardized presentation of heavy-metal contents in most sediments. An ex- 692 32 - 28 - 2U 16 ^m in samples from the same location is given in Fig. 1. To characterize such a group of co-genetic sediments, the linear

relationships can be extrapolated to 100% or 50% of the fraction < 16/xm. Also, the fractions < 20 and < 63 urn, and the specific surface areas, have been used in correlation studies of heavy metals in different sediment fractions (Lichtfuss& Brummer 1977; Smithet al. 1973). The calculation of a regression line, however, requires a large number (10-15) of samples from one location. Moreover, it is often impossible to determine a regression line, due to the limited range in grain size of the sediment at a certain location. Another way to treat grain size corrections is to isolate a certain granular fraction, and analyze the metals within such a fraction (A). Separation of grain sizes is advantageous, because only a few samples from a particular location are needed. However, the separation of the fractions less than 2, 16 or 20 /im is time-consuming; moreover the method requires resuspension in (distilled) water, which may cause remobilization of metals. On the other hand, separation of the fraction less than, for instance, 204 or 175 /im by sieving has the disadvantage that the separated fractions contain considerable amounts of large grains, which are usually low in trace metals (Förstner & Salomons 1980). It has therefore been proposed to use the < 63 pm fraction for comparisons of metal contents (Förstner and Salomons, 1980). The advantages are: 1) Trace metals have been found to be present mainly in the clay/ silt particles; 2) This fraction is nearly equivalent to the material carried in suspension; 3) Sieving does not alter metal concentrations by remobilization; 4) Numerous studies on metals have been performed on the < 63 ^ m fraction; 5) Comparisons among the metal concentrations in muddy sediments and in coarser sediments (e.g. those from the sea floor) are possible. Separations of the fractions < 63 ^m are performed either by dry- or by wet-sieving. Dry-sieving is possible only if the sample has been freeze-dried. The use of disposable nylon sieves, a method developed by the Rouen Municipal Laboratory (France), is recommended by the Centre Océanologique de Bretagne (France). Care should be taken to sieve just enough sediment, with a minimum of water. The combined water and sieved sediment should be oven-dried at 40 ° C. Another way (C) to eliminate grain size is to normalize the metal concentrations to the amount of 'conservative' elements such as aluminum. This method has the disadvantage of giving ratio values instead of real concentrations but, at present, there is insufficient data to determine the

difference between the concentrations derived by the use of methods (B) and (C). If only small quantities of sediment sample are available, e.g. in the case of suspended matter, metal/Al ratios may be a good alternative, because the Al contents can be determined on small amounts of material and often in the same extracts as those for the heavy-metal determinations. 693 Chemical partition To assess the impact of contaminated sediments on the environment, information on total concentrations, alone, are not sufficient. Only a part of the metals present may take part in short-time geochemical processes or may be bio-available. For this reason, a series of different extraction procedures have been devised to gain a more or less detailed insight into the distribution of metals within the various chemical compounds and minerals. A summary of several methods is given in Table 1. Various single leaching steps are combined into leaching schemes to determine trace metals in sediments, e.g. differentiation of trace metals into a reducible, an oxidizable and a resistant fraction; a distinction between exchangeable metals, metals present in metal hydroxide coatings, organic solids, and the crystal phase; determination of metal contents in interstitial water and in exchangeable, easily reducible, moderately reducible, organic and residual fractions. It should be pointed out that the extraction procedures are not as selective as is sometimes stated. Re-adsorption of metals may take place and the results are influenced by the duration of the experiment, the temperature and the ratio of solid matter to volume of extraction solution. Unfortunately there is a proliferation of extraction schemes, which also make it difficult to compare the results of analyses. Therefore a 'standard extraction scheme' has been prepared by Salomons & De Groot (1978) and summarized as follows: 1) An extraction with 0.1 M hydroxylamine-HCl. This step includes the extraction of exchangeable cations and of carbonate-bound metals; 2) An extraction with acidified peroxide (30%). This extraction should be followed by an extraction with ammonium acetate to remove any reabsorbed metal ions; 3) Dissolution of the remaining sample with HF to estimate the metals left in the residual fraction. The rather important 'exchangeable phase' (representing very loosely bound trace metals which regulate or reflect the composition of surface waters) is not included in this scheme. To determine the amount of exchangeable metal ions, an

extractant is used which contains cations that are more strongly bound, than metals, to the exchange sites (BaCl2, MgCl2 and NH4OAc). Although the ionexchangeable fraction of trace metals is ill-defined, ammonium acetate is a generally accepted agen

## CHAPTER III. CONTENT ANALYSIS

### 3.1. Content analysis of antacids

**Content analysis (from the English contents - content, content) or content analysis is a standard research method in the field of social sciences, the subject of analysis**

**of which is the content of text arrays and products of communicative correspondence.**

In the domestic research tradition, content analysis is defined as a quantitative analysis of texts and text arrays with the aim of subsequent meaningful interpretation of the identified numerical patterns. Content analysis is used in the study of sources that are invariant in the structure or essence of the content, but externally exist as unsystematized, randomly organized text material. The philosophical meaning of content analysis as a research method consists in the ascent from the diversity of textual material to an abstract model of the content of the text (conceptual-categorical apparatus, ambiguity, collisions, paradoxes). In this sense, content analysis is one of the nomothetic research procedures used in the field of application of idiographic methods. There are two main types of content analysis: quantitative and qualitative.

The content analysis technique has found wide application in the information age, but the history of the method is not limited to the era of automatic text processing. So the first examples of the use of content analysis date back to the 18th century, when in Sweden the frequency of the appearance of certain topics in the text of a book served as a criterion for its hereticalness. However, it is possible to speak seriously about the use of content analysis as a full-fledged technique only since the 30s of the XX century in the United States.

The term content analysis was first used in the late XIX - early. XX centuries. American journalists B. Matthew, A. Tenney, D. Speed, D. Whipkins. At the origins of the formation of the methodology of content analysis was also the French journalist J. Kaiser. Content analysis was used mainly in sociological research, including in the study of advertising and propaganda materials.

In the field of political research, the use of the method of content analysis was initiated by G. Lassuel, who analyzed propaganda materials from the Second World War. In the 1960s, during the so-called "methodological explosion", research using the method of content analysis became especially active. This contributed to the development of the technique, diversified its options. It was during this period that the active use of computer technology in research began.

The range of disciplines in which content analysis is used is quite wide. Ole Holsti gives the following distribution of research in the field of content analysis by sciences: sociology, anthropology - 27.7%, communication theory - 25.9%, political science - 21.5%. It should also be noted the application of content analysis in the field of historical research and public relations.

With the help of content analysis, it is possible to analyze such various types of texts as media reports, statements of politicians, party programs, legal acts, advertising and propaganda materials, historical sources, literary works.

A prerequisite for the application of the content analysis methodology is the availability of a material carrier of information. In all cases where such a medium exists or can be recreated, it is permissible to use the content analysis technique.

**First step**

**Determination of the set of studied sources or messages using a set of specified criteria that each message must meet:**

• a given type of source (press, television, radio, advertising or propaganda materials)
• one type of messages (articles, notes, posters);
• specified parties involved in the communication process (sender, recipient (recipient);
• comparable message size (minimum size or length);
• frequency of occurrence of messages;
• the way messages are disseminated;
• place of distribution of messages;
• time of appearance of messages.

Other criteria can be used if necessary, but the ones listed above are the most common.

**Second phase**

Formation of a sample of messages. In some cases, it is possible to study the entire set of sources determined at the first stage, since the cases (messages) to be analyzed are often limited in number and readily available. However, sometimes content analysis must rely on a limited sample taken from a larger body of information.

**Third stage**

Identification of units of analysis. They can be words or themes. The correct choice of units of analysis is an important part of the whole work. The simplest element of a message is a word. A topic is another unit that is a separate statement about a subject. There are quite clear requirements for the choice of a possible unit of analysis:

• it must be large enough to express meaning;

• it should be small enough not to express many meanings;

• it must be easily identifiable;

• the number of units must be so large that it is possible to make a sample of them If a topic is chosen as a unit of analysis, then it is also allocated in accordance with some rules:

**Fourth stage**

Allocation of counting units, which may coincide with semantic units or be of a specific nature. In the first case, the analysis procedure boils down to calculating the frequency of mentioning the selected semantic unit, in the second, the researcher, on the basis of the material being analyzed and the goals of the research, himself nominates the counting units, which can be:

• the physical extent of the texts;

• text area filled with semantic units;

• number of lines (paragraphs, characters, columns of text);

• duration of broadcast on radio or TV; Absolute frequency of mention, times

• footage of a film for audio and video recordings,

• the number of drawings with a certain content, plot, etc. In some cases, researchers use other counting elements as well. Of fundamental importance at this stage of content analysis is the strict definition of its operators.

**Fifth stage**

**Directly the counting procedure. In general, it is similar to the standard methods of classification by selected groupings. The compilation of special tables, the use of computer programs, special formulas, statistical calculations are applied.**

Usually tables of the form are compiled:

| Analysis units | Analysis units | Account units | Account units |
|---|---|---|---|
| **Categories** | **Subcategories** | **Absolute frequency of mention, times** | **Reference frequency is relative , %** |
| 1 Categories | 01 subcategory | 15 | 32 |
| | 02 subcategory | 7 | 15 |
| | 03 subcategory | 25 | 53 |
| Total: | | 47 | 100 |

• The subject cannot go beyond the bounds of the paragraph.

• A new topic arises if there is a change:

o perceiver,

o current,

o goals,

o categories.

There are also special methods of content analysis, adapted to the needs of historical and historical-philosophical research.

**Sixth stage**

Interpretation of the results obtained in accordance with the goals and objectives of a particular study. Usually, at this stage, such characteristics of the text material are identified and evaluated, which allow making conclusions about what the author wanted to emphasize or hide. It is possible to identify the percentage of prevalence in society of the subjective meanings of an object or phenomenon

Quantitative content analysis (also called meaningful) is based on the study of words, topics and messages, focusing the attention of the researcher on the content of the message. Thus, when intending to analyze the selected elements, one must be able to foresee their meaning and determine each possible result of observation in accordance with the expectations of the researcher.

In practice, this means that as a first step in conducting this type of content analysis, the researcher must create a kind of vocabulary in which each observation will be defined and assigned to the appropriate class.

The problem is that the researcher must anticipate not only the mentions that may occur, but also the elements of their contextual use, and for this a detailed system of rules for assessing each use case must be developed. This task is usually solved by piloting the set of messages to be analyzed (that is, by identifying on the material a small sample of messages of those types of key mentions that are most likely to occur in a subsequent, more complete analysis) in combination with arbitration assessments of contexts and ways of using terms. It is preferable to deal with the observations of not one, but several researchers.

A more difficult task is the need to ascribe specific assessments to key references - when we have to decide whether a given reference is given in a positive or negative sense, "for" or "against" the object of interest to us, etc., and also when we it is necessary to rank a number of references according to the strength of their assessments (i.e., in accordance with which of them is the most positive, which is the next in terms of positiveness, etc.). At the same time, the researcher needs sufficiently subtle indicators that could measure not only the moods of political subjects, but also the strength of these moods. The fulfillment of this task is especially difficult in historical, historical-philosophical and psychological research, since it presupposes a high level of humanitarian training of specialists using the method of content analysis. There are many methods to make this decision easier. In some cases, they rely on the judgments of a group of arbitrators (experts) about the meaning or strength (intensity) of a term. Examples of such techniques include the Q-sorting method and pairwise comparison scaling. At the turn of XX-XXI centuries. specialists in the application of mathematical

methods in historical research paid much attention to the development of special computer expert systems (within the framework of the ideology.

**Q-sort method**

Q-grading uses a nine-item rigid distribution scale: item 1 corresponds to the lowest intensity of the trait being measured (for example, the least degree of approval), and item 9 corresponds to the highest degree of intensity (for example, the highest degree of approval). The goal here is to simply rank (order) all judgments along a single evaluative axis. The arbiter is given a certain rigid quota for each category of the scale (that is, the expected number of words or phrases that should be classified by him in this category), and then he is asked to distribute a given set of terms so that the established quotas are not violated. Quotas are based on the assumption (not necessarily true) that fluctuations in the intensity of words and phrases should fit within the normal distribution (when the cases under study are maximally concentrated in the middle of the scale, and as one moves towards its poles, their number decreases steadily). The arbitrators, therefore, are forced to give relative assessments of specific words and phrases (cases), referring them to certain categories of the scale.

After the arbitrators have completed their work, the arithmetic mean of the scale is calculated for each case, and then the resulting mean ratings are ranked accordingly. Further, the results of this ranking of cases in terms of intensity are used to assign codes to the analyzed texts, due to the occurrence of words in them or topics that have received our assessment. The arbitrariness of one researcher's assessment is thus compensated for by the presence of other opinions.

**Pairwise comparison scaling**

Scaling by the paired comparison method has the same goals as the previous method, but its technique is somewhat different. Each case to be assessed is sequentially compared in pairs with all other cases, with each arbiter deciding which of the words (or phrases) in each pair is “stronger” (or more intense) than the other. So, if it is necessary to compare five statements (cases), then each arbiter will sequentially compare first the 1st of them with the 2nd, with the 3rd, 4th, 5th, then the 2nd with the 3rd, 4th, 5th, etc., each time noting which of the two is more intense. By calculating

how many times each case was “stronger” in the assessment of all arbitrators, and dividing the resulting number by the number of arbitrators (that is, calculating the average assessment given by the group of arbitrators to each statement), we get the opportunity to quantitatively rank all cases according to their intensity. The higher the average score of a certain statement, the more “stronger” it is, in the opinion of the arbitrators.

However, there are at least two complexities associated with Q-sort and pairwise comparison. First, in both of these cases, the researcher relies entirely on the decisions of the arbitrators, the criteria for assessing which may or may not be legitimate and / or consistent. In the examination of this kind of standards are not always clear or, in any case, not always clearly defined, and as a result, the assessments themselves are debatable. There are cases when the same arbiter gives different marks to the same statement in a series of identical tests. Moreover, the selection of arbitrators is highly arbitrary. Consequently, the reliability of the results obtained by relying on such arbitrators is very relative. Therefore, these procedures should be used, taking into account the "human factor".

**Quality content analysis**

In addition to words, themes and other elements that designate the content side of messages, there are other units that allow for a qualitative or, as it is also called, structural content analysis. In this case, the researcher is interested not so much in what is said as in what is said.

For example, the task may be to find out how much time or print space was devoted to a subject of interest in a particular source, or how many words or newspaper columns were given to each of the candidates during a certain election campaign.

On the other hand, other, possibly more subtle issues related to the form of the message can be taken into account: is a particular newspaper message accompanied by a photograph or some kind of illustration, what are the dimensions of the headline of this newspaper message, is it printed on the front page or is it placed among the numerous advertising messages. When answering such questions, the attention of the researcher is focused not on the intricacies of the content, but on the way the message is presented.

The main question here is the fact of the presence or absence of material on the topic, the degree of its emphasis, its size, and not the nuances of its content. As a result of such analysis, measurements are often much more reliable than in the case of content-oriented research (since formal indicators are less ambiguous), but, as a result, they are much less significant.

Measurements in the parameters studied in the course of qualitative content analysis superficially affect the very content of each message, in contrast to the detailed and careful examination required in quantitative analysis. As a result, high-quality content analysis is usually easier to design and conduct, and therefore cheaper and more reliable than meaningful content analysis.

And although his results may be less satisfying, since they provide a sketch rather than a complete picture of the message, when answering a specific research question, they can often turn out to be quite adequate.It is known that the development of the pharmaceutical industry over the years of independence is mainly aimed at the development of import-substituting drugs using local raw materials, or their combination with an innovative approach. In this case, special attention is paid to highly effective drugs in rational dosage forms (DF). (1) Suspensions are of particular interest in terms of their properties. The object of the study is the nomenclature of antacid drugs presented in the State Register of Medicines of the Republic of Uzbekistan.

In conducting the content analysis, as an object of research, we took into account the data on the registration of medicinal products based on the materials of the State Register of Medicines and Medical Products' for the period of 2019. We also used data from the Vidal Handbook, Medicines in Uzbekistan, List of Essential Medicines, and others. (8,9)

3.2 A pharmaceutical suspension is a coarse dispersion of insoluble solid particles in a liquid medium. The particle diameter in a suspension is usually greater than 0.5 μm. However, it is difficult and also impractical to impose a sharp boundary between the suspensions and the dispersions having finer particles. Suspensions are an important class of pharmaceutical dosage forms. The advantages

of suspension dosage forms include effective dispensing of hydrophobic drugs; avoidance of the use of cosolvents; masking of unpleasant taste of certain ingredients; offering resistance to degradation of drugs due to
hydrolysis, oxidation or microbial activity; easy swallowing for young or elderly patients; and efficient intramuscular depot therapy. In addition, when compared to solution dosage forms, relatively higher concentration of drugs can be incorporated into suspension products. The present review provides an overview of various aspects of suspensions such as classification of suspensions, theories of suspensions, various suspending agents, formulations aspects of suspensions, packaging of suspensions, evaluation of suspensions, stability of suspensions and recent research work that is being carried on suspensions.

A Pharmaceutical suspension is a coarse dispersion in which internal phase is dispersed uniformly throughout the external phase. The internal phase consisting of insoluble solid particles having a specific range of size which is maintained uniformly throughout the suspending vehicle with aid of single or combination of suspending agent. The external phase (suspending medium) is generally aqueous in some instance, may be an organic or oily liquid
for non oral use.

Classification

1. Based on General Classes

- Oral suspension
- Externally applied suspension
- Parenteral suspension

2. Based on Proportion of Solid Particles

- Dilute suspension (2 to10%w/v solid)
- Concentrated suspension (50%w/v solid)

3. Based on Electro Kinetic Nature of Solid

- Particles
- Flocculated suspension
- Deflocculated suspension

4. Based on Size of Solid Particles

- Colloidal suspension (< 1 micron)
- Coarse suspension (>1 micron)
- Nano suspension (10 ng)

Pharmaceutical suspensions are liquid dosage forms containing finely divided insoluble materials (the suspensoid) distributed somewhat uniformly throughout the suspending medium (suspending vehicle) in which the drug exhibits a minimum degree of solubility. This dosage form is used for providing a liquid dosage form for insoluble or poorly soluble drugs. Also, it is an ideal dosage form for drugs that are unstable in an aqueous medium for extended periods of time. Such drugs are most frequently supplied as dry powder for reconstitution at the time of dispensing. Technically, the term suspension describes a dispersion of a solid material (the dispersed phase) in a liquid (the continuous phase) without reference to the particle size of the solid material. However, the particle size of the solid material can affect both its physicochemical behaviour of suspensions. For this reason, a distinction is usually made between a colloid or colloidal suspension with a particle size range of up to about 1 micron, and a ‘coarse dispersion’ with larger particles. Unfortunately, pharmaceutical suspensions fall across the borderline between colloidal and coarse dispersions, with solid particles generally in the range of 0.1 to 10 micrometre. Suspensions are not optically clear and will appear cloudy unless the size of the particles is within the colloidal range.

In an ideal suspension, insoluble particulate matter or drugs are uniformly suspended in three dimensions throughout the vehicle and remain so even after prolonged periods of time. Here, every dose from the suspension will contain the same amount of drug

and will give the same clinical effect to the patient. This, however, is practically not possible because of the thermodynamic instability of suspension.

Suspension dosage forms are given by the oral route, injected intramuscularly or subcutaneously, instilled intranasally, inhaled into the lungs, applied to the skin as topical preparations, or used for ophthalmic or otic purposes in the eye or ear, respectively. Some suspensions are available in a ready-to-use form that is, already distributed through a liquid vehicle with or without stabilizers and other additives. Other preparations are available as dry powders intended for reconstitution just before use with an appropriate vehicle. Generally, this type of product is a powder mixture containing the drug and suitable suspending and dispersing agents to be diluted and agitated with a specified quantity of vehicle, most often purified water. n addition to the use of aqueous pharmaceutical suspensions as drug products, suspensions are also used as in-process materials during industrial pharmaceutical manufacturing. For example, tablets are coated with a suspension of insoluble coating materials. Granules manufactured by wet granulation processes are typically suspended in the air for drying during fluidized bed-drying process. In addition, wet granulation could be carried out on granules suspended in the air in a process called fluid-bed granulation.

Ideal features of suspension dosage form

1. The final product should be physically, chemically and microbiologically stable.
2. Pharmaceutical suspension should be aesthetically pleasing and should also have a pleasing odour, and taste.
3. Suspended particles should be small and uniformly sized in order to give a smooth, elegant product free from a gritty texture.
4. The product must remain sufficiently homogenous for at least the period between shaking the container and removing the required amount.
5. Suspensions must not be too viscous to pour freely from a bottle or to flow through a needle syringe (for injectable suspensions).

6. All the doses dispensed from a given multi-dose container should have acceptable uniformity of drug content.
7. The drug substance must not recrystallize and/or change its polymorphic form during storage.
8. Suspended particles should settle slowly and the sediment or creaming produced on storage, if any, should readily redisperse upon gentle shaking of the container.
9. Parenteral and ophthalmic suspensions should be sterilizable and syringable (for parenteral suspensions).
10. Parenteral suspensions should be isotonic and non-irritating.

In the case of an external lotion,

11. The product must be fluid enough to spread easily over the affected area but not so fluid that it runs off the surface too quickly.
12. The suspension must dry quickly and provide an elastic protective film that will not rub off easily.

Sedimentation volume (F) or height (H) for flocculated suspensions:

$$F = V_u / V_o \text{ ---------- (A)}$$

Where, $V_u$ = final or ultimate volume of sediment

$V_o$ = original volume of suspension before settling.

Sedimentation volume is a ratio of the final or ultimate volume of sediment (Vu) to the original volume of sediment (V) before settling. Some time 'F' is represented as 'Vs' and as expressed as percentage. Similarly when a measuring cylinder is used to measure the volume

$$F = H_u / H_o$$

Where, $H_u$ = final or ultimate height of sediment

$H_O$ = original height of suspension before settling Sedimentation volume can have values
ranging from less than 1 to greater than1; F is normally less than 1. F=1, such product is said
to be in flocculation equilibrium. And show no clear Supernatant on standing Sedimentation
volume (F) for deflocculated suspension

$F_¥ = V_¥ / V_O$

Where,$F_¥$ =sedimentation volume of deflocculated suspension

$V_¥$ = sediment volume of completely deflocculated suspension.

(Sediment volume ultimate relatively small)

$V_O$=Original volume of suspension .

### 3.2. Antacids are a group of medications that are widely used to neutralize excess stomach acid

They temporarily raise the pH of gastric contents to relieve heartburn and the pain of peptic ulcer in many patients. Heartburn is a characteristic symptom of gastro-esophageal reflux disease (GERD); it is a burning sensation that results from the flow of acidic stomach contents into the distal esophagus. Antacids also provide relief from the discomfort of acid reflux since any regurgitated stomach contents are no longer acidic in nature . Since antacids neutralize stomach acid, they reduce the amount of acid reaching the duodenum. They also inhibit the activity of the proteolytic enzyme pepsin . Consequently, antacids can relieve pain and pylorospasms, inhibit protein digestion, and prevent corrosion by acidic chyme .

Antacids can be classified as systemic or non-systemic. Those with a systemic effect are highly soluble in aqueous media. As a result, they are rapidly absorbed from the gastrointestinal tract (GIT) after consumption and may cause systemic alkalosis. A typical example is sodium bicarbonate. Conversely, non-systemic antacids are less soluble in aqueous media and, hence, exert their effect locally in the GIT. Examples

include aluminum hydroxide, calcium carbonate, calcium hydroxide, magaldrate, magnesium trisilicate, magnesium oxide, and magnesium hydroxide . Typically, antacids contain one or more of these active ingredients.

According to the Joint Formulary Committee , calcium-containing antacids can induce rebound acid secretion. They can also precipitate the milk-alkali syndrome and induce hypercalcemia and alkalosis if high doses are consumed over a prolonged period. Magnesium- and aluminum-containing antacids also tend to have laxative and constipating effects, respectively. Antifoaming agents such as simethicone (activated dimethicone) are sometimes added to antacids to relieve flatulence. Additionally, such preparations are useful for the relief of hiccup in palliative care. Alginates are added to some antacid preparations because they form a viscous gel, typically termed “raft”, floats on gastric contents to protect the esophageal mucosa from acid reflux. Antacids that contain alginates can also increase the viscosity of stomach contents

One principal characteristic of an antacid is effective acid neutralization, which can be determined in vitro via an acid-neutralizing capacity (ANC) test . The ANC of an antacid is the amount of hydrochloric acid that the antacid can neutralize. It is worth noting that the ANCs of preparations that contain more than one antacid may be the same as those of simpler preparations

Antacids have been on the market globally for several years, as they were originally the first-line medications for managing peptic ulcer disease ; however, the discovery of other treatments such as inhibitors of gastric acid production and secretion, specifically, proton-pump inhibitors and $H_2$ receptor blockers, has transformed the management of peptic ulcer disease. Prescription medications are also available for GERD and other causes of dyspepsia; however, antacids are usually in high demand due to the ease of self-treatment . Although the global age-standardized prevalence of GERD was stable from 1990 to 2017, it was at 8,791 and 8,819 cases per 100,000 population, respectively. Additionally, the disease was responsible for 0.7% of all years lived with disability globally in 2017. These are indications of the global burden of the disease and the demand for antacid treatments.

Antacid doses recommended by manufacturers vary; however, they must be adjusted based on patient age and the presence of other comorbidities such as renal or hepatic impairment. Additionally, since antacids do not require a prescription, they are sometimes used improperly with little to no relief of symptoms. According to Salisbury and Terrell , it is important to educate patients on the importance of the right mode and time of administration of antacids, as well as the right dosage for prompt and prolonged relief of symptoms. Nevertheless, it should be noted that antacids only provide symptomatic relief, which may mask an underlying condition. Additionally, although they do not cause clinically significant toxicities when administered in high doses, it is essential to understand interactions between antacids and other medicines since they may have significant effects on patient health. This is particularly important among polypharmacy patients

Antacids are usually available commercially as solid dosage forms and suspensions. However, the liquid preparations are largely preferred because the smaller particle size and greater surface area of their active ingredients can result in a better and faster action

Patients may be more likely to choose an antacid that is cost-effective, palatable, and effective at a low volume. Additionally, a physician should usually consider that an antacid has a high ANC (expressed in milliequivalents), neutralizes the greatest volume of acid per unit cost, and is palatable and easy to consume before prescribing it for a patient

Due to the relatively easier regulatory restrictions surrounding the manufacture and use of antacids, the medicines consumer market continues to experience the influx of new antacid products, with attendant quality, efficacy and safety concerns. Therefore, it is needful to regularly assess the quality of existing ones and share such reports with stakeholders. The outcomes of such evaluations can guide selection of the best products and inform the relevant regulatory agencies on the quality of these medicines.

In recent times, only two studies have reported on the quality of antacids in Ghana, with one considering only their ANCs and the second considering their ANCs and buffering capacities . The samples considered in these studies were collected from

Accra and Kumasi, the two major cosmopolitan cities in the country. This shows how limited quality-related information exist on a class of medicines that continue to enjoy high patronage and potential abuse among medicine consumers. To this end, authors in the present study, aimed to extend the knowledge on the quality of these products by considering samples from a different urban setting, Ho (where no previous knowledge exists on the quality of these products being consumed there) and expanding the scope of investigations to include other parameters that tend to influence the choice of these products. Thus, the relationship between ANC and cost, sedimentation characteristics, pH, density, and viscosity were considered in a multivariate analytical approach. Additionally, we adopted a standardized checklist tool, modified from existing ones in literature to visually inspect the samples and propose its adoption for routine use in the future assessments of antacids and other medicines.

Evaluation of pH and density

The pH of each antacid was determined using a calibrated digital pH meter (model ST3100-F; OHAUS Corporation, Parsippany, NJ, USA). Each antacid was well shaken, after which 10 mL of the suspension was transferred into a 25 mL beaker for pH measurement. The relative density of each mixture was determined using a pycnometer. All measurements were performed at room temperature. Triplicate determinations were performed for each sample.

Determination of flow time and viscosity

The time taken for 10 mL of each suspension to flow through a 10 mL pipette was determined. The viscosities of the samples were determined using a digital rotary viscometer (A & E Lab Instruments Co., Ltd., Guangzhou, China). The test was performed using spindle no. 2 and at a speed of 30 rpm. The test was performed on 100 mL of adequately agitated suspension. Triplicate determinations were performed for each sample in each test at room temperature.

Evaluation of sedimentation volume and rate

After adequate shaking to obtain a homogeneous mixture, 50 mL of the samples were carefully transferred into separate 50 mL measuring cylinders. The samples were left

untouched for 12 days at room temperature on the laboratory bench. Sediment volume was recorded hourly up to 7 hours on day 1, and then on days 2, 3, 4, 5, 6, 7, and 12 [18]. Triplicate determinations were performed for each sample. Sedimentation volume was estimated as the ratio of equilibrium volume of sediment (i.e., final sediment volume) to the total volume of suspension. A graph of sediment volume against time was plotted for each sample. Sedimentation rate was estimated as the slope of the line of best fit for each plot.

Determination of ANC

ANC was determined as described in the United States Pharmacopeia and National Formulary [19]. First, a sample was well shaken until its contents were uniform. An accurately measured quantity of the uniform suspension equivalent to the minimum dose indicated on the bottle label was then transferred into a 250 mL beaker. Water was added to the sample to obtain a 70 mL mixture, which was then stirred on a magnetic stirrer for 1 minute. Next, an accurate volume of 30 mL of 1.0 N HCl was added to the suspension, followed by stirring of the mixture for 15 minutes. An additional 30 mL of the HCl was added to samples that had pH $\geq$ 3.5 after the first addition of HCl. Excess HCl was titrated against 0.5 N NaOH until a pH of 3.5 was obtained. The number of milliequivalents (mEq) of acid consumed by each antacid was calculated using the following equation:

$$\text{Total mEq} = (V_{HCl} \times N_{HCl}) - (V_{NaOH} \times N_{NaOH})$$

Where $N_{HCl}$ and $N_{NaOH}$ are the normalities of HCl and NaOH, respectively, and $V_{HCl}$ and $V_{NaOH}$ are the volumes of HCl and NaOH, respectively.

Data analysis

Data have been expressed as mean ± standard deviation. GraphPad Prism for Windows (version 8.0.2; GraphPad Software, Inc., La Jolla, CA, USA) and Minitab (version 18.1; Minitab Inc., State College, PA, USA) were used for data analysis. Student's *t*-test and analysis of variance were used to assess differences in physicochemical parameters. A correlation analysis was performed to evaluate the relationship among the parameters. Spearman's correlation (ρ) and corresponding *p*-values were determined using Student's *t*-test at 95% confidence level.

Data were further explored using principal component analysis (PCA) and hierarchical clustering analysis (HCA). PCA was conducted to reduce the dimensionality of the data matrix and determine principal components (PCs), which can explain variabilities in parameters. Eigenanalysis of the correlation matrix of the dataset was used to compute eigenvectors. PCs with loadings greater than 1 were considered significant. HCA was performed using Ward's linkage method and squared Euclidean distance to confirm the clusters observed from the PCA score plot.

Visual inspection of products

The findings of the visual inspection are presented in Table 1. It was noted that external/secondary packaging was intact and contained information on active ingredients and their amounts for products that had it. Samples G, K, L, M, and N were in plastic bottles but they did not have secondary packaging for additional physical protection. The same products did not also have any dosing devices. Consequently, patients may use household devices for dose measurement, which may lead to inaccurate dosing. This may not be ideal because it has been proven in previous studies that household teaspoons and tablespoons are unreliable dosing devices [20, 21]. Inaccurate dosing can result in underdosing and no improvement of symptoms, or overdosing and its attendant effects, even though the active ingredients in antacids do not typically cause clinically significant toxicities when administered in high doses [5]. Two products (M and N) did not have storage information on their labels. Although all product details on all labels were legible, some information on more than half of the labels were not indelible, meaning such products were at risk of being falsified. We determined indelibility by rubbing the labels with cotton wool soaked with ethanol (96%) five times. A label was considered delible if any part of it was completely removed after the test. Four of the locally produced antacids (K, L, M, and N) did not have trade names, while only two imported products (B and G) had registered trade names.

All the antacids had information on their active ingredients, dosage, and manufacturing and expiry dates on their internal packaging. Only sample N did not have the amounts of active ingredients stated on its label. All products were contained in bottles with

intact and airtight closures. Samples K and M did not have any batch numbers indicated on them, which does not conform with good manufacturing practices as such products cannot be traced.

Although some products failed few of the visual inspection tests, it does not necessarily mean that the observations correlate with poor physicochemical qualities. However, such checklists are important attributes of the quality control of pharmaceutical products. Moreover, the results of the inspection may be a fairly good indicator of chemical non-conformities of the products [15].

**Antacid samples and reagents**

A comprehensive list of liquid antacids available in retail community pharmacies in the Ho Municipality of the Volta Region of Ghana was compiled, from which 14 different brands were randomly sampled. All the products were purchased on the same day and labeled A−N.

Analytical grade HCl and NaOH were obtained from VWR International SAS (Fontenay-sous-Bois, France) and Eurostar Scientific Ltd. (Liverpool, England) for the study.

The room temperature over the study period was 29.6 ± 1.2 °C.

Visual inspection of the samples

All the products were inspected using a modified and objective checklist based on the inspection tools developed by the Department of Quality Assurance and Safety of Medicines of the World Health Organization and Schiavetti *et al*. Items in the tools for evaluating solid dosage forms were removed to obtain the final checklist, which was well suited to the products being investigated. The evaluation was done to visually inspect the antacids as a quality check for improper packaging, labelling, and missing information about the strengths of active ingredients, dosage, and expiration date, amongst others.

Antacids are a class of drugs used to treat conditions caused by the acid that is produced by the stomach. The stomach naturally secretes an acid called hydrochloric acid that helps to break down proteins. This acid causes the contents of the stomach to be

acidic in nature, with a pH level of 2 or 3 when acid secretion is active. (pH levels are a measure of acidity in the stomach: the lower the number, the greater the acidity.) The stomach, duodenum, and esophagus are protected from acid by several protective mechanisms. When there is too much acid or protective mechanisms are inadequate, the lining of the stomach, duodenum or esophagus may become damaged by the acid, giving rise to inflammation and ulcerations and their various gastrointestinal symptoms such as

- nausea,
- abdominal pain, and
- heartburn (due to gastroesophageal reflux disease or GERD).

Antacids reduce acidity by neutralizing (counteracting) acid, reducing the acidity in the stomach, and reducing the amount of acid that is refluxed into the esophagus or emptied into the duodenum. Antacids also work by inhibiting the activity of pepsin, a digestive enzyme produced in the stomach that is active only in an acid environment and, like acid, is believed to be injurious to the lining of the stomach, duodenum, and esophagus.

It is important to note that when antacids are taken on an empty stomach they provide acid reduction for 20 to 40 minutes only because the antacid is rapidly emptied into the duodenum.

- When taken after a meal, (approximately 1 hour afterward) antacids reduce acid for at least three hours since food from the meal slows the emptying of the antacid (and food) from the stomach.
- It is important to discuss the use of antacids with a physician or pharmacist, especially if used in combination with other prescribed medications so as to avoid drug interactions.

Antacids are used commonly for symptoms such as

- heartburn,
- abdominal pain (sometimes described as the sour stomach), and
- nausea resulting from a number of conditions such as
  - inflammation or
  - acid-peptic ulcers of the esophagus (esophagitis),
  - stomach (gastritis), and
  - duodenum (duodenitis)

*What are the types of antacids?*

- Aluminum carbonate antacids can be used to treat and manage hyperphosphatemia (abnormally elevated levels of phosphate in the blood) since they bind phosphate in the intestine and prevent it from being absorbed into the body. Because of this ability to bind phosphate in the intestine, aluminum carbonate antacids also can be used with a low phosphate diet to prevent the formation of kidney stones, since kidney stones are made up of various elements including phosphates.
- Calcium carbonate antacids are used in conditions of calcium deficiency such as postmenopausal osteoporosis since some of the calcium is absorbed into the body.
- Magnesium oxide antacids are used to treat magnesium deficiencies from either diets or medications that cause magnesium depletion.
- Off-label (not FDA-approved) uses for antacids containing aluminum and magnesium or aluminum alone include preventing bleeding from stress-induced ulcers. Other off-label uses for antacids are treatment and maintenance of healing of duodenal ulcers and treatment of gastric ulcers.

ARE THERE ANY DIFFERENCES AMONG THE DIFFERENT TYPES OF ANTACIDS?

Some antacid products may neutralize more acid in the stomach than others. The way to express the ability of an antacid to neutralize acid is by determining the antacid's neutralizing capacity (ANC). The ANC is expressed as milliequivalents (mEq) of acid

that is neutralized, and it measures the ability of the antacid to neutralize acids (to a ph of 3.5 to 4). Per FDA requirements, an antacid must have a neutralizing capacity of ≥5 mEq per dose. The most effective antacids should have a high acid neutralization capacity and rapid gastric acid neutralization qualities.

- Antacids such as sodium bicarbonate and calcium carbonate have the greatest neutralizing capacity but are not used for long periods of time due to adverse events. (Please see the sections on warnings/precautions and side effects.)

An antacid's onset of neutralizing action (how fast the drug dissolves in gastric acid) varies among different antacids.

- Sodium bicarbonate and magnesium hydroxide dissolve quickly and provide a rapid buffering effect,
- while aluminum hydroxide and calcium carbonate dissolve slowly.
- Antacid suspensions generally dissolve more easily than tablets or powders. If a tablet antacid is used, however, it is advisable to chew the tablets thoroughly for maximal effectiveness.

Another difference amongst the antacids is the duration of action (how long it continues to neutralize acid in the stomach).

- Sodium bicarbonate and magnesium hydroxide have the shortest duration of neutralizing action,
- while aluminum hydroxide and calcium carbonate have the longest.
- Combination aluminum magnesium antacids have an intermediate duration of action.

WHAT ARE THE SIDE EFFECTS OF ANTACIDS?

- Antacids may cause dose-dependent rebound hyperacidity and milk-alkali syndrome.
- Antacids that contain aluminum hydroxide may cause constipation, aluminum-intoxication, osteomalacia, and hypophosphatemia.

- Antacids that contain magnesium have a laxative effect that may cause diarrhea, and in patients with renal failure they may cause increased magnesium levels in the blood, because of the reduced ability of the kidneys to eliminate magnesium from the body in the urine.

WHAT ARE THE WARNINGS AND PRECAUTIONS FOR ANTACIDS?

- Antacids (for example, calcium carbonate) when consumed in high doses and for long periods of time may cause acid rebound. Acid rebound is a condition in which the stomach produces even more acid after the consumption of foods and drinks. Fortunately, the effects of acid rebound are not clinically important.
- High-dose calcium carbonate and sodium bicarbonate when taken together can cause a condition called milk-alkali syndrome. Its symptoms include headache, nausea, irritability, and weakness, hypercalcemia (high blood calcium levels), and reduced function of the kidneys.
- Extensive use of aluminum-containing antacids may cause hypophosphatemia (low phosphate levels in the blood), which in severe cases could lead to muscle weakness, anorexia, and osteomalacia (softening of the bones due to defective bone mineralization).
- Antacids containing aluminum hydroxide should be used with caution in patients who have recently suffered massive upper gastrointestinal bleeding.
- For patients with conditions such as high blood pressure, chronic heart failure, renal failure and those who have sodium or salt-restricted diets, it is important to pay attention to the sodium level in sodium-based antacid preparations such as sodium bicarbonate
- Antacids should not be given to children under six years of age.

WHAT ANTACIDS ARE AVAILABLE?

- AlternaGEL (liquid)
- Aluminum Hydroxide

- Aluminum Hydroxide Gel (suspension)
- Aluminum-magnesium hydroxide sulfate (Magaldrate)
- Amphojel (tablets)
- Calcium acetate (PhosLo tablets)
- Calcium carbonate
- Citra pH (solution)
- Concentrated Aluminum Hydroxide Gel (suspension)
- Concentrated Aluminum Hydroxide Gel (liquid)
- Concentrated Phillips' Milk of Magnesia (liquid)
- Dialume (capsules)
- Dulcolax (Liquid)
- Isopan (Liquid)
- Mag-Ox 400 (tablets)
- Magnesium Hydroxide
- Magnesium Oxide
- Magnesium Oxide (tablets)
- Magaldrate (liquid)
- Maox 420 (tablets)
- Milk of Magnesia (liquid)
- Phillips' Chewable (tablets, chewable)
- Uro-Mag (capsules)
- Riopan (suspension)
- Sodium Bicarbonate
- Sodium Citrate

Antacid combinations

- Alka-Seltzer Effervescent Tablets,
- Alamat Suspension,
- Bromo Seltzer Effervescent Granules
- Gaviscon Extra Strength Antacid,

- Gaviscon Liquid,
- Gas-X with Maalox Extra Strength Tablets,
- Maalox Regular Strength Liquid,
- Mylanta Antacid Gelcaps,
- Rolaids Tablets, and
- Titralac Extra Strength Tablets,

# CHAPTER IV. DEVELOPMENT OF SUSPENSION QUALITY CONTROL METHODS

## 4.1. Development of quality control methods for a suspension containing aluminum and magnesium hydroxides

Determination of aluminum ions in the "Almidosis" suspension.

Content:

Magnesium hydroxide (gel) 600 mg

Aluminum hydroxide (gel) 525 mg.

Description: White, or almost white, milk-like liquid with a menthol odor. Authenticity: When diluting 1 ml of solution to 10 ml with purified water, qualitative reactions were carried out for aluminum ions.

Aluminum ion: 1) Washed out the precipitate obtained in the identification test with a hot solution of ammonium chloride (1 in 50) and dissolve the precipitate in hydrochloric acid and add 1 ml of thioacetamide reagent, no precipitate was formed. Then diluted sodium hydroxide solution was added dropwise; a gel-like white precipitate was formed, which dissolved upon the subsequent addition of a diluted sodium hydroxide solution. A solution of ammonium chloride was gradually added to the resulting solution, and a gel-like white precipitate was again formed. Conclusion: Suspension "Almidoz" fully complies with the requirements of the State Pharmacopoeia XI to determine the authenticity of aluminum ions.

Determination of magnesium ions in the "Almidosis" suspension.

Authenticity: after dilution of 1 ml of a solution with 10 ml of purified water, a qualitative reaction was carried out for the magnesium ion.

Magnesium ion: 1 ml of ammonium chloride, 1 ml of ammonia and 0.5 ml of sodium phosphate solution were added dropwise to 1 ml of the solution until a soluble precipitate was formed in dilute mineral acids. Conclusion: the resulting suspension "Almidoz" fully complies with the requirements of the State Pharmacopoeia XI in determining the authenticity of the magnesium ion.

Separation of layers for suspensions.

The separation time of the layers after shaking the suspension should be at least 5 minutes.

**Table 1**

| № | Time, min. |
|---|---|
| 1 | 4,9 min |
| 2 | 4,8 min |
| 3 | 5 min |
| 4 | 5 min |
| 5 | 4,9 min |

Conclusion: The time of separation of layers after shaking the resulting suspension "Almidoz" fully complied with the requirements of SP XI.

Suspension of syringes.

The suspension should easily pass from the 0840 needle to the syringe.

**Table 2**

| № | Igna | Past |
|---|---|---|
| 1 | 0440 | I failed |
| 2 | 0840 | passed |
| 3 | 0860 | I failed |
| 4 | 0640 | I failed |
| 5 | 1060 | I failed |

Conclusion: The resulting suspension "Almidoz" was transferred from the 0840 needle into a syringe. GF XI complied with the requirement.

## 4.2. Determination of the pharmaceutical equivalence of a suspension containing aluminum and magnesium hydroxides

It is necessary to effectively control the quality of preparations containing metals. Therefore, to improve the quality control of drugs and drug detection methods, high accuracy and selectivity for the development of new, more advanced analytical methods that can detect drugs in a wide range of specific components with low material costs. problem.

When choosing a drug control method, a number of requirements are taken into account: sufficient selectivity, the absence of a complicated sampling process, the minimum possible research time, sufficient versatility (the possibility of multi-element analysis), and the minimum weight of equipment. The research is aimed at increasing the consistency and expressiveness of the analyzes carried out.

The aim of the study was to check the pharmaceutical equivalence of the Maalox suspension, which is the bioequivalent of the Almidoz suspension containing aluminum and magnesium hydroxides, produced by the JV LLC Jurabek laboratories.

**Table 3**

| **"Almidoz" "Maalox"** | **"Almidoz" "Maalox"** | **"Almidoz" "Maalox"** |
|---|---|---|
| Composition magnesium hydroxide (in the form of a gel) 600 mg; | Composition magnesium hydroxide (in the form of a gel) 600 mg; | Composition magnesium hydroxide (in the form of a gel) 600 mg; |
| Description white or almost white milky | Description white or almost white milky suspension with | Description white or almost white milky suspension |

| | | |
|---|---|---|
| suspension with menthol odor White or almost white milky suspension with menthol odor | menthol odor White or almost white milky suspension with menthol odor | with menthol odor White or almost white milky suspension with menthol odor |
| Authenticity | 1. To 5 ml of the solution was added 10 ml of diluted hydrochloric acid and 5 drops of methyl red, heated to boiling, 6 N ammonium hydroxide was added until the color of the solution turned dark yellow, then continued boiling for 2 minutes, filtered: the filtrate responds to magnesium tests. To the resulting solution was added 1 ml of diluted ammonia solution, a white precipitate was formed, dissolved in ammonium chloride.<br>2. Washed out the precipitate obtained in the identification test with a hot solution of ammonium chloride (1 in 50) and the precipitate was dissolved in hydrochloric acid and 1 ml of thioacetamide reagent was added. No | 1) When diluting 1 ml of the solution to 10 ml with purified water, a qualitative reaction was carried out for aluminum ions.<br>Aluminum ion: The precipitate obtained in the identification test with a hot solution of ammonium chloride (1 in 50) was washed away and the precipitate was dissolved in hydrochloric acid and 1 ml of thioacetamide reagent was added. No precipitate was formed. Then diluted sodium hydroxide solution was added dropwise; a gel-like white precipitate was formed, which dissolved upon the subsequent addition of a diluted sodium hydroxide solution. A solution of ammonium |

| | | |
|---|---|---|
| | precipitate was formed. Then diluted sodium hydroxide `solution was added dropwise; a gel-like white precipitate is formed, which dissolves upon the subsequent addition of a diluted sodium hydroxide solution. A solution of ammonium chloride was gradually added to the resulting solution, and a gel-like white precipitate was again formed. the solution meets the aluminum test. | chloride was gradually added to the resulting solution, and a gel-like white precipitate was again formed. the solution meets the aluminum test.<br>2) When diluting 1 ml of the solution to 10 ml with purified water, a qualitative reaction was carried out for magnesium ions.<br>Magnesium ion: 1 ml of ammonium chloride, 1 ml of ammonia and 0.5 ml of sodium phosphate solution were added dropwise to 1 ml of the solution until a soluble precipitate was formed in dilute mineral acids. |
| Quantitation | *Aluminum. To 10 ml of the drug was added 30-40 ml of diluted hydrochloric acid and heated until complete dissolution. Cooled and transferred to a 100 ml flask, made up to the mark with water for injection and mixed. 5 ml of the resulting solution* | *Quantitative determination of aluminum hydroxide. To 10 ml of the drug was added 30-40 ml of hydrochloric acid and heated until complete dissolution. It was cooled and transferred to a 100 ml bottle, labeled with water for injection and* |

| | | |
|---|---|---|
| | *was transferred into a conical flask with a capacity of 250 ml, 25.0 ml of sodium edetate 0.05 M and 10 ml of acetate buffer solution pH 4.5 and 30 ml of ethanol and 2 ml of freshly prepared 0.25 g / L solution of dithizone in ethanol.* An excess of sodium edetate was titrated with a 0.05 M solution of zinc sulfate until the solution changed from greenish-blue to red-violet.<br>1 ml of 0.05 M zinc sulfate solution corresponds to 0.00390 g of hydrated aluminum oxide.<br>The content of hydrated aluminum oxide (Al $(OH)_3$) in 1 ml of the drug solution should be from 0.0475 to 0.0575 g.<br>*Magnesium hydroxide. To 10 ml of the drug was added 30-40 ml of diluted hydrochloric acid and heated until complete dissolution. Cooled and transferred to a 100 ml flask, adjusted to the mark with* | *mixed. 5 ml of the resulting solution was transferred into a 250 ml conical vial, 25.0 ml of sodium edetate 0.05 M and 10 ml of an acetate buffer solution pH 4.5 and 30 ml of the test solution, and 2 ml of a freshly prepared solution of dithizone 0.25 μg / L ethanol was added ...* The titrated excess of sodium edetate was titrated with 0.05 ml of zinc sulfate solution until the solution changed from greenish blue to reddish purple. 1 ml of 0.05 m zinc sulfate solution corresponds to 0.00390 g of aluminum hydroxide. The analysis results are presented in the table.<br>*Quantitative determination of magnesium hydroxide. To 10 ml of the drug was added 30-40 ml of hydrochloric acid and heated until complete dissolution. It was cooled* |

| | | |
|---|---|---|
| | *water for injection. 2 ml of the resulting solution was transferred into a conical flask with a capacity of 500 ml, 200 ml of water for injection and 20 ml of an ammonia buffer solution pH 10.9 and 50 mg of eriochrome black indicator were added.* Titrated with 0.05 M solution of Trilon B until the transition from violet color of solution to blue.<br>1 ml of 0.05 M zinc sulfate solution corresponds to 0.002916 g of magnesium hydroxide.<br>The content of magnesium hydroxide (Mg (OH) 2) in 1 ml of the drug solution should be from 0.0570 to 0.0630 g. | *and transferred to a 100 ml bottle labeled with water for injection. A volume of 2 ml of the resulting solution was transferred into a 500 ml conical vial, 200 ml of water and 20 ml of an ammonia buffer solution for injection at pH 10.9 and 50 mg of the primary indicator of eriochrome were used.* Titrate 0.05 m of Trilon B solution until the color of the solution changes from purple to blue. 1 ml of 0.05 m zinc sulfate solution corresponds to 0.002916 g of magnesium hydroxide [3]. |
| Main pharmacological effects Antacid Antacid | Main pharmacological effects Antacid Antacid | Main pharmacological effects Antacid Antacid |

Conclusions. The pharmaceutical equivalence of the Maalox suspension, which is the bioequivalent of the Almidoz suspension containing aluminum and magnesium hydroxides, produced by Jurabek Laboratories JV LLC, was investigated.

## 4.3. Quantification and statistical processing of the analysis of the "Almidosis" suspension

The composition of the suspension "Almidoz":

Active Ingredients:

magnesium hydroxide (gel) 600 mg;

aluminum hydroxide (in the form of a gel) 525 mg;

Description: White or almost white suspension with a milky menthol odor.

Quantitative determination of aluminum hydroxide. To 10 ml of the preparation add 30-40 ml of hydrochloric acid and heat until complete dissolution. It was cooled and transferred to a 100 ml bottle, labeled with water for injection and mixed. 5 ml of the resulting solution was transferred into a 250 ml conical vial, 25.0 ml of sodium edetate 0.05 M and 10 ml of an acetate buffer solution pH 4.5 and 30 ml of the test solution, and 2 ml of a freshly prepared solution of dithizone 0.25 μg / L ethanol was added ... The titrated excess of sodium edetate was titrated with 0.05 ml of zinc sulfate solution until the solution changed from greenish blue to reddish purple. 1 ml of 0.05 m zinc sulfate solution corresponds to 0.00390 g of aluminum hydroxide. The analysis results are presented in Table 4.

**Tab. 4**

**Results of quantitative determination of hydrated aluminum and some metrological characteristics**

| № | $X_n$ | X | d | $S^2$ | S | $S_X$ | R | Q | ΔX | Δ X | ε | έ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0,5244 | 0,52424 | 0,00016 | 0,0000058 | 0,002408 | 0,00107 | 0,0014 | 0,714 | 0,00134 | 0,0006 | 0,25% | 0,11% |
| 2 | 0,5234 | | 0,00084 | | | | | 0,571 | | | | |
| 3 | 0,5242 | | 0,00004 | | | | | 0,428 | | | | |
| 4 | 0,5248 | | 0,00056 | | | | | 0,286 | | | | |
| 5 | 0,5244 | | 0,00016 | | | | | | | | | |

**Tab. 5**

**Results of quantitative determination of hydrated aluminum and some metrological characteristics**

| N° | F | $x_{cp}$ | $S^2$ | S | P | t(P,f) | $\Delta X_{cp}$ | $\varepsilon_{cp, \%}$ |
|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| | 4 | 0.5244 | 0.0000058 | 0.002408 | 95 | 2.78 | 0.00134 | 0.25% |

As can be seen from the table, the method for the quantitative determination of hydrated aluminum by the complexometry method was 0.25%, which does not exceed the limits of the method.

Statistical processing of the results of quantitative analysis of aluminum hydroxide in the "Almidoz" suspension.

$X_1$= 0,5244

$X_2$= 0,5234

$X_3$= 0,5242

$X_4$= 0,5248

$X_5$= 0,5244

n= 5

f=n – 1 = 5 – 1 = 4

1) Determine the arithmetic mean.

The ratio of the sum of several numbers to the number of additions to these numbers.

$X=\frac{0,5244+0,5234+0,5242+0,5248+0,5244}{5}$=0,52424

2) Determination of the deviation from the average result.

The range of possible parameter values can be specified when adding or editing a parameter. The task range ensures that the parameter value is within the specified range of values. The minimum and maximum values are determined for the series.

$d_1$= |0,5244-0,52424| = 0,00016

$d_2$= |0,5234-0,52424| = 0,00084

$d_3$= |0,5242-0,52424| = 0,00004

$d_4$= |0,5248-0,52424| = 0,00056

$d_5$= |0,5244-0,52424| = 0,00016

3) Determination of variance

The variance gives information about the return of the obtained values, and to calculate it, we first determine the range of values - d and the value of the degree of freedom - f.

$S^2 = \frac{(0,00016+0,00084+0,00004+0,00056+0,00016)}{4} = 0,0000058$

4) Determination of the standard deviation

Standard deviation is the theory of probability and statistics, the most common indicator of the distribution of random variables relative to their mathematical expectation. Usually, these terms refer to the square root of a random variable, but sometimes they can refer to one or more options for estimating a value.

$S= \sqrt{S} = \sqrt{0,0000058} = 0,002408$

5) Standard deviation from the mean

The standard deviation from the mean is the theory of probability and statistics, the most common indicator of the distribution of random variables relative to their mathematical expectation. Usually, these terms refer to the square root of a random variable, but sometimes they can refer to one or more options for estimating a value.

$S_x= \frac{S}{\sqrt{n}} = \frac{0,002408}{\sqrt{5}} = 0,00107$

6) Control criterion

When the number of analyzes performed n <10, homogeneity of values can be determined without calculating a statistical description. For this, the practical value of the control criterion is -Q, which is compared with the theoretical value of the control criterion.

R - range of values

$R = |X_1 - X_n|$

$R = |0,5248 – 0,5234| = 0,0014$

$Q_1 = \frac{|0,5244-05234|}{0,0014} = 0,714$

$Q_2 = \frac{|0,5234-05242|}{0,0014} = 0,571$

$Q_3 = \frac{|0,5242-05248|}{0,0014} = 0,428$

$Q_4 = \frac{|0,5248-05244|}{0,0014} = 0,286$

7) Range of reliability

How close X is to A is determined by the confidence interval

X + ΔX

$\Delta X = S \times t(P,f) = 0,002408 \times 2,78 = 0,00134$

8) Half Confidence Interval

$\Delta X = \frac{\Delta X}{\sqrt{n}} = \frac{0,00134}{2,236} = 0,0006$

9) Relative error

Relative error is the value at which the mean absolute error is measured by representing what part of the mean

expressed as a percentage.

$\varepsilon = \frac{\Delta X}{X} \times 100\% = \frac{0,00134}{0,52424} \times 100\% = 0,25\%$

10) Determine the average relative error

$\acute{\varepsilon} = \frac{\Delta X}{X} \times 100\% = \frac{0,0006}{0,52424} \times 100\% = 0,11\%$

Quantitative determination of magnesium hydroxide. To 10 ml of the drug was added 30-40 ml of hydrochloric acid and heated until complete dissolution. The solution was cooled and transferred to a 100 ml vial, diluted with water for injection. A volume of 2 ml of the resulting solution was transferred into a 500 ml conical vial, 200 ml of water and 20 ml of an ammonia buffer solution for injection at pH 10.9 and 50 mg of the primary indicator of eriochrome were used. Titrated with 0.05 m of Trilon B solution to blue color. 1 ml of 0.05 m zinc sulfate solution corresponds to 0.002916 g of magnesium hydroxide.

Statistical processing of the results of quantitative analysis of magnesium hydroxide in the "Almidoz" suspension.

$X_1$= 0,5966

$X_2$= 0,5960

$X_3$= 0,5959

$X_4$= 0,5964

$X_5$= 0,5965

n= 5

f=n – 1 = 5 – 1 = 4

1) Determine the arithmetic mean

The ratio of the sum of several numbers to the number of additions to these numbers.

$X=\frac{0,5966+0,5960+0,5959+0,5964+0,5965}{5}=0,59628$

2) Determining the range of values

The range of possible parameter values can be specified when adding or editing a parameter. The task range ensures that the parameter value is within the specified range of values. The minimum and maximum values are determined for the series.

$d_1$= |0,5966-0,59628| = 0,00032

$d_2$= |0,5960-0,59628| = 0,00028

$d_3$= |0,5959-0,59628| = 0,00038

$d_4$= |0,5964-0,59628| = 0,00012

$d_5$= |0,5965-0,59628| = 0,00022

3) Determination of variance

The variance gives information about the return of the obtained values, and to calculate it, we first determine the range of values - d and the value of the degree of freedom - f.

$S^2 = \frac{(0,00032+0,00028+0,00038+0,00012+0,00022)}{4} = 0,0000032$

4) Determination of the standard deviation

Standard deviation is the theory of probability and statistics, the most common indicator of the distribution of random variables relative to their mathematical expectation. Usually, these terms refer to the square root of a random variable, but sometimes they can refer to one or more options for estimating a value.

$S= \sqrt{S} = \sqrt{0,0000032} = 0,001816$

5) Standard deviation from the mean

The standard deviation from the mean is the theory of probability and statistics, the most common indicator of the distribution of random variables relative to their

mathematical expectation. Usually, these terms refer to the square root of a random variable, but sometimes they can refer to one or more options for estimating a value.

$S_x = \frac{S}{\sqrt{n}} = \frac{0,001816}{\sqrt{5}} = 0,000812$

6) Control criterion

When the number of analyzes performed n <10, homogeneity of values can be determined without calculating a statistical description. For this, the practical value of the control criterion is - Q, which is compared with the theoretical value of the control criterion.

R - range of values

$R = |X_1 - X_n|$

$R = |0,5966 – 0,5959| = 0,0007$

$Q_1 = \frac{|0,5966-0,5960|}{0,0007} = 0,857$

$Q_2 = \frac{|0,5960-0,5959|}{0,0007} = 0,143$

$Q_3 = \frac{|0,5959-0,5964|}{0,0007} = 0,714$

$Q_4 = \frac{|0,5964-0,5965|}{0,0007} = 0,143$

7) Range of reliability

How close X is to A is determined by the confidence interval

$X + \Delta X.$

$\Delta X = S \times t(P,f) = 0,001816 \times 2,78 = 0,001$

8) Half Confidence Interval

$\Delta X = \frac{\Delta X}{\sqrt{n}} = \frac{0,001}{2,236} = 0,00044$

9) Relative error

The relative error is the value at which the average absolute error is measured by representing how much of the average is expressed as a percentage.

$\varepsilon = \frac{\Delta X}{X} \times 100\% = \frac{0,001}{0,59628} \times 100\% = 0,17\%$

10) Determine the average relative error

$\acute{\varepsilon} = \frac{\Delta X}{X} \times 100\% = \frac{0,00044}{0,59628} \times 100\% = 0,07\%$

Table 3

Results of statistical processing of quantitative analysis of hydrated magnesium and some metrological properties.

## 4.1. Study of the stability of a suspension containing aluminum and magnesium hydroxides

To date, monotherapy with antacids - metal salts is practically not used. Modern antacids contain a balanced complex of active substances that compensate for each other's shortcomings. Most often, they include magnesium salts, which have a laxative effect, and aluminum salts, which have a fixing effect [1, 3].

Pharmaceutical enterprises of Uzbekistan also produce a suspension containing calcium and magnesium hydroxides.

The quality, therapeutic efficacy and safety of drugs during storage directly depend on the ability of drugs to maintain properties within the limits established by regulatory documents (ND) for a certain period under appropriate storage and transportation conditions, i.e. from its stability.

Based on the results of the stability study, the shelf life and storage conditions of the drug are established, the materials used and the type of primary and secondary packaging are selected, which are indicated in the ND and in the instructions for medical use, and also taken out on the packaging.

Methods for studying the stability of drugs are based on determining their quality under certain conditions for a certain time [1, 3]. The determination of the shelf life was carried out in vivo in accordance with the guidelines for the study of stability and the establishment of the shelf life of new substances and finished medicinal products.

To study the stability, samples of dosed powders were stored under natural conditions at a temperature of 25 ° C in a dry, dark place. V

During storage, the analysis of powders was periodically carried out according to the following indicators: "Description", "Average mass of powders and deviations from the average mass", "Quantification". The results of the analysis of the suspension are presented in table 6.

**Table 6**

**Results of analysis (description, quantification) of an oral suspension containing aluminum and magnesium hydroxides during natural storage**

| Shelf life, years | Description | Quantity definition |
|---|---|---|
| 6month | White cloudy solution | 0,525/0,600 |
| 1 year | Complies with | 0,524/0,598 |
| 2 years | Complies with | 0,523/0,599 |
| 2 years 6 months | Complies with | 0,524/0,599 |
| 3 years | Complies with | 0,525/0,600 |

From the data in Table 1, it can be seen that during three years of natural storage there was a slight decrease in the quantitative content of calcium and magnesium. The oral suspension was found to be stable for three years. This shelf life was laid down in the draft of the pharmacopoeial monograph of the enterprise.

Thus, their stability was studied under natural storage conditions at a temperature of 25 ° C in a dry, dark place, and the shelf life was determined - 3 years.

Thus, the stability of a suspension containing calcium and magnesium hydroxides was studied by the method of classical aging. The suspension was stored in a dry, dark place at a temperature of 25 ° C. During natural storage, experimental samples were periodically analyzed. As a result, the shelf life of the medicinal product was set at 3 years.

## CHAPTER IV. STUDY OF THE STABILITY OF A SUSPENSION CONTAINING ALUMINUM AND MAGNESIUM HYDROXIDES

**Table 7**

| | $X_n$ | X | D | $S^2$ | S | $S_X$ | R | Q | ΔX | ΔX | ε | έ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0,5966 | 0,59628 | 0,00032 | 0,0000032 | 0,001816 | 0,000812 | 0,0007 | 0,857 | 0,001 | 0,00044 | 0,17% | 0,07% |
| 2 | 0,5960 | | 0,00028 | | | | | 0,143 | | | | |
| 3 | 0,5959 | | 0,00038 | | | | | 0,714 | | | | |
| 4 | 0,5964 | | 0,00012 | | | | | 0,143 | | | | |
| 5 | 0,5965 | | 0,00022 | | | | | | | | | |

## CONCLUSIONS AND OFFERS

The developed suspensions "Almidoz" fully complied with the requirements of the State Pharmacopoeia XI. A structured content analysis of antacid drugs was carried out by comparing the quantitative and qualitative characteristics according to the criteria: dosage form, pharmacotherapeutic group, origin, by far abroad countries, CIS, domestic. It was shown that the market was dominated by domestic drugs 7.8%, CIS – 9.4%, foreign manufacturers 9.8%; antiseptic - domestic - 16.3%, CIS - 7.6%, foreign - 3.2%.

Work is underway to develop control methods, regulatory documents for implementation in domestic industrial pharmacy in order to obtain import substitute drugs for the Republic of Uzbekistan.

5. Studied the stability of a suspension containing calcium and magnesium hydroxides by the method of classical aging. The suspension was stored in a dry, dark place at a temperature of 25 ° C. During natural storage, experimental samples were periodically analyzed. As a result, the shelf life of the medicinal product was set at 3 years.

## LIST OF USES


1. Legal documents and publications of methodological significance.
2. Decree of the President of the Republic of Uzbekistan dated February 7, 2017 No PF-4947 "On the Action Strategy for the five priority areas of development of the Republic of Uzbekistan in 2017-2021" .// www.lex.uz
3. Resolution of the President of the Republic of Uzbekistan dated February 14, 2018 No PP-3532 "On additional measures for the accelerated development of the pharmaceutical industry" .//www.lex.uz
4. Resolution of the President of the Republic of Uzbekistan dated May 6, 2019 No PP-4310 "On measures to further develop the system of medical and pharmaceutical education and science" ////lex.uz
5. Monographs, scientific articles, patents, scientific publications.
6. Bobakulov T.I. Ensuring the stability of the national currency: problems and solutions. Monograph, Tashkent: “SCIENCE AND TECHNOLOGY” 2017. 184 p. (Monograph)
7. Ispolzovannaya drugaya literatura.

8. L.Alekseev, V.TT. Course kachestvennogo ximicheskogo polumikroanshshza: Kr. spravochnik / V.N. Alekseev M: Gos.ximizdat, 1973. - 586 p.
9. Alekseev, V.N Kolichestvennyy analiz: Kr. sprav. / V.N. Alekseev M .: Gos.ximizdat, 1952. - 574 p.
10. Almagel-neo in the treatment of functional dyspepsia and flatulence / M.R. Konno rev, A.M. Litvyakov, N.N. Sholoxova, V.N. Rakov // Med. news. 2003. - № 2. - S.61 - 64.
11. Balabudkin, M.A. Rotorno-pulsatsionnye apparaty v khimiko-farmatsevticheskoy promыshlennosti / M.A. Balabudkin M., 1983. - p. 92-100; 130-142.
12. Baranskaya, E.K. Pariet v lechenii yazvennoy bolezni / E.K. Baranskaya // Klinich. perspectives of gastroenterology, hepatology. - 2001. - № 5. - p. 26-
13. Beygel, M.Z. Determination of the size of the frequency in suspensions of zinc-insulin by the method of mutation / M.Z. Beygel, N.N. Soboleva, V.I. Trofimov // Xim. farmats. jury. - 1985. - № 11. - p. 1395 - 1400.
14. Belenkiy, M.A. Element kolichestvennoy otsenki pharmacologicheskogo effekta / M.A. Belenkiy L .: Med. lit., 1963. - 152s.
15. Belokon, I.F. Izuchenie tochnosti dozirovaniya suspenziy dlya detey / I.F. Belokon // Pharmacy. 1989. - T. 38, № 1. - p. 68 - 69.
16. Bibik, R. Otsenka mikrobiologicheskogo kachestva kosmeticheskix preparations / Bibik R., Martintsov I. // Farmaceuticky review. 1986. - T.55, № 4. -S. 147-156.
17. Bolezni pishchevoda i jeludka / Red. F.I. Komarov et al.-M., 1995. 220s.
18. Bondarenko, A.I. K voprosu o stepeni dispersnosti lekarstvennyx veshchestv v farmatsevticheskix suspenziyax / A.I. Bondarenko // Pharmacy. 1982. - № 4. - p. 27 - 30.
19. Borisochkina L.I. Antioxidants, preservatives, stabilizers, dyes, flavors and aromatic substances in fish promыshlennosti / L.I. Borisochkina M .: Pishch. prom-st, 1976. - 182 p.

20. Brejneva, N.M. K voprosu polucheniya ustoychivyx suspenziy iz sulfanilamidnyx preparations / N.M. Brejneva, N.A. Kuprina // Vsssoyuz. s'ezd farmatsevtov (1; 1967; Pyatigorsk): Tr. . M., 1970. - p. 599 -605.
21. Bulgakov, S. A. Rasshirenie vozmojnostey lecheniya yazvennoy bolezni pri ispolzovanii sovremennyx antatsidnyx preparations; S.A. Bulgakov // Klinich. pharmacology and therapy. 1998. - T. 1, № 1. - p. 14 - 16.
22. Sh. Buresh, B .Ya. Metodiki i osnovnye eksperimenty po izucheniyu mozga i povedeniya / Buresh B.Ya., Bureshova O.K. - M., Vyssh. shk., 1991. - p. 119122.
23. Vasilev,. Yu.V. Modern antacid preparations in gastroenterologic practice / Yu.V. Vasilev // Lech. vrach -2004. №4 - C. 18 - 23.
24. Influence of flow turbulence on vozniknovenie and development of cavitation / TO.JL Levkovskiy, A.V. Chalov // Active Journal. 1978. - T \ 24, vyp. 2. -S. 221 -227.
25. Vyyavlenie piloricheskix kampilobakterov / IlchenkoA.A., Smotrova I.A., Zhukhovitskiy V.G., Aruin L.I. // Sov. med. 1990. - N 4. -S. 19-23.
26. Gaevyy, M.D. Pharmacotherapy with the basics of clinical pharmacology: Ucheb. dlya uchashchixsya farmats. VUZov / Gaevyy M.D., Galenko-Yaroshevskiy P.A., Petrov V.I. Volgograd, 1996. - p. 204 - 207; 214216.
27. Dick, I.G. Gidrodinamicheskaya model uskoreniya sedimentatsii melkix chastits v bidispersnoy suspenzii / I.G. Dick, L.L. Minkov, T. Neesse // Thermophysics and aeromechanics. 2001. - T. 8, № 1.- S. 283 - 294.
28. Gorbakov, V.V. Sravnitelnaya characteristics of antisekretornyx preparations of various groups according to daily rN — monitoring /
29. B.V. Gorbakov, Yu.S. Makarov, T.V. Golochalova // Lech. vrach 2001. -№ 5 - 6. - p. 11.
30. Gosudarstvennaya pharmacopoeia of the USSR. -X izd. - M .: Medicine, 1968. —1. C. 1079.
31. Gosudarstvennaya Pharmacopoeia of the USSR: Vyts. 1. General methods of analysis / MZ USSR. 11-e izd., Dop. - M: Medicine, 1987. - 336 p.

32. Gosudarstvennaya Pharmacopoeia of the USSR: Vyp.2. General methods of analysis / MZ USSR. -11-e izd., Dop. M: Medicine, 19S7. - 398 s.
33. Gradus, L.Ya. Guidance on dispersion analysis by microscopy method / L.Ya. Gradus - M., 1979. - 28 p.
34. Grakovskaya, L. K. Suspension as a medicinal form / L.K. Grakovskaya, G.B. Barsheva // Vseros. Congress of Pharmacists (4; 1981; Voronezh): Materials. Voronezh, 1981. - p. 272 - 274.
35. Grigorev, P.Ya., Diagnosis and treatment of diseases of the digestive organs / Grigorev P.Ya., Yakovenko E.GT. -M .: Medicine, 1996. 508 p.
36. Grigorev, P.Ya., Spravochnoe rukovodstvo po gastroenterologii / Grigorev P.Ya., Yakovenko A.V. -M., 1997. 410 p.
37. Golbrayx, JI.C. Xitin and xitozan: stroenie, svoystva, primenenie / L.S. Golbrayx // Sorosovskiy obrazovat. jurn. 2001. - T. 7, № 7. -S. 51-56.
38. Davydova, V.A. Izuchenie vozmojnosti solyubilizatsii nekotoryx gidrophobnyx veshchestv / V / A. Davydova // Vseros. Congress of Pharmacists (4; 1981; Voronezh): Materials. Voronezh, 1981. - S 275 - 276.
39. Diagnostics, treatment and prevention of exacerbations and complications of acid-dependent and Helicobacter-dependent diseases: Method, instructions / MZRF-M., 1997.-30 p.
40. Dilbarkhanov, R.D. On the issue of obtaining stable medicinal suspensions / R.D. Dilbarkhanov, G.S. Bashura, Z.R. Safiulina // Congress of Pharmacists Kaz. SSR (2; 1981; Chimkent): Abstracts. report Chimkent, 1981. -S. 340-341.
41. Evstratova K.I. Physical and colloidal chemistry: Textbook. For farm. universities and faculties / Evstratova K.I., Kupina N.A., Malakhova E.E. M .: Higher. tick., 1990 .-- S. 451 - 453.
42. Ermolaeva, V.E. Trilonometric determination in the Reney catalyst / V.E. Ermolaeva, N.I. Frolova, G.E. Burtsev // Chem. pharmacy. zhurn. - 1976 .-- T. 10, t 10 - S. 134 - 136.
43. Zlatkina, A.R. Pharmacotherapy of chronic diseases of the digestive system / A.R. Zlatkina. M., 1997 .-- 240 p.

44. Children's health in Russia / Ed. A.A. Baranova M., 1999 .-- S. 66-92.
45. Zupants, N.B. Experimental substantiation of the use of glucose-amine and its derivatives in medicine: Dis. in the form of scientific. report ... dr. honey. sciences. / N. B. Zupants. Kupavna, 1993 .-- S. 42 - 43.
46. Ivatsgkin ^ V.T. Antacids: mine therapy or a component of antiulcer treatment in the clinic of internal diseases / V.T. Ivashkin // New effective drugs. - M .: TOP-Med, 1997. Issue. 1. -C. 31.
47. Izmerov, N.F. Parameters of toxicometry of industrial poisons with a single exposure: Handbook / Izmerov N.F., Sanotskiy I.V., Sidorov K.IC. M .: Medicine; 1977 .-- 170 p.
48. Zyubr, T.P. The use of aerosil to stabilize suspensions of hydrophilic substances / T.P. Zyubr, E.M. Mishchenko // Vseros. Congress of Pharmacists (5; 1987; Yaroslavl). Abstracts. report Yaroslavl ,, 19S7. - S. 143 - 144.
49. Kozmin, V.D. Using the Rebinder effect to intensify the production of pharmaceutical suspensions / V.D. Kozmin // Vseros. Congress of Pharmacists (4; 1981; Voronezh): Materials. Voronezh, 1981.- S. 276-277.
50. Kapralov, N.V. Antisecretory efficacy of omez in the treatment of peptic ulcer disease according to the results in the inside of the gastric pH monitoring / N.V. Kapralov, I.A. Sholomitskaya, A.V. Savchenko // Med. news. —2002.1.-S. 55-56.
51. Kinasov, D.G. Creation of a corrected suspension of anti-aging action / D.G. Kinasov // Gastroenterology of St. Petersburg -2003. No. 2 -Z.-S. 128.
52. Knore, D.G. Physical chemistry: Textbook. for biol. f. tov universities and ped. Universities / Knore D.G., Krylova L.F., Musicians B.C. - M .: Higher. shk., 1990.-419 p.
53. On the issue of obtaining fine substances in the production of suspensions / B.I. Vakushin, V.A. Eremin, A.E. Ripko, E.G. Glushko // All-Union. Congress of Pharmacists (3; 1980; Chisinau): Abstracts of reports. Chisinau, 1980, p. 79-80.

54.Kozmin, V.D. Using the Rebinder effect to intensify the production of pharmaceutical suspensions / V.D. Kozmin // All-Ros. Congress of Pharmacists (4; 1981; Voronezh): Materials. Voronezh, 1981.-S 276-277.
55.Kozmin, V.D. Theoretical foundations for the selection of surfactants for the stabilization of pharmaceutical suspensions / V.D. Kozmin // All-Union. Congress of Pharmacists (3; 1980; Chisinau): Abstracts. report Chisinau, 1980 .-- P. 81.
56.Kozmin, V.D. On the use of surfactants to obtain thin emulsions and suspensions / V.D. Kozmin // Congress of Pharmacists of Georgia (1; 1978; Tbilisi): Materials. Tbilisi, 1978 .-- C259 - 262.
57.Kolb, V.G. Handbook of clinical chemistry / Kolb V.G., Kamyshanov B.C. - Minsk, 1982. -425 p.
58.Vikulova S. Bioequivalence and generics are made for each other. Remedium, 1999. © 12.S. 30-32.
59.Methodical recommendations for conducting high-quality clinical studies of bioequivalence of medicinal products. M., Ministry of Health of the Russian Federation, 2001.- 24 p.
60.Meshkovsky A.P. WHO recommendations in the field of determining the equivalence of generic drugs. Pharmateca, 1996. © 3.S. 3-7.
61.Shcherbakov V. WHO interferes in the production of generics. Remedium, 2000. © 3.P. 57-60.
62.Hussain AS, et al. The Biopharmaceutics Classification System: Highlights of the FDA's Draft Guidance Office of Pharmaceutical Science, Center for Drug Evaluation and Research, Food and Drug Administration.
63.Mills D (2005). Regulatory Agencies Do Not Require Clinical Trials To Be Expensive International Biopharmaceutical Association: IBPA Publications.
64.FDA CDER Office of Generic Drugs - further U.S. information on bioequivalence testing and generic drugs.
65. Birkett D (2003). Generics - equal or not? Aust Presc 26 (4): 85-7.

66. Food and Drug Administration (2003). Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations. Rockville (MD): FDA.
67. EMEA, CPMP, Note for Guidance on the investigation of Bioavailability and Bioequivalence, London, July 2001 CPMP / EWP / QWP / 1401/98.
68. Medical Dissertations http: // medical diss.com/farmakologiya/razrabotka tehnologii i issledovanie suspenzii antatsidnogo deystviya na osnove alyuminiya i magniya gidroksidov # ixzz6ee6d2xds
69. Izmerov, N.F. Parameters of toxicometry of industrial poisons with a single exposure: Handbook / Izmerov N.F., Sanotskiy I.V., Sidorov K.IC. M .: Medicine; 1977 .-- 170 p.
70. Zyubr, T.P. The use of aerosil to stabilize suspensions of hydrophilic substances / T.P. Zyubr, E.M. Mishchenko // Vseros. Congress of Pharmacists (5; 1987; Yaroslavl). Abstracts. report Yaroslavl ,, 19S7. - S. 143 - 144.
71. Kozmin, V.D. Using the Rebinder effect to intensify the production of pharmaceutical suspensions / V.D. Kozmin // Vseros. Congress of Pharmacists (4; 1981; Voronezh): Materials. Voronezh, 1981.- S. 276-277.
72. Kapralov, N.V. Antisecretory efficacy of omez in the treatment of peptic ulcer disease according to the results in the inside of the gastric pH monitoring / N.V. Kapralov, I.A. Sholomitskaya, A.V. Savchenko // Med. news. —2002.1.-S. 55-56.
73. Kinasov, D.G. Creation of a corrected suspension of anti-aging action / D.G. Kinasov // Gastroenterology of St. Petersburg -2003. No. 2 -Z.-S. 128.
74. Knore, D.G. Physical chemistry: Textbook. for biol. f. tov universities and ped. Universities / Knore D.G., Krylova L.F., Musicians B.C. - M .: Higher. shk., 1990.-419 p.
75. On the issue of obtaining fine substances in the production of suspensions / B.I. Vakushin, V.A. Eremin, A.E. Ripko, E.G. Glushko // All-Union. Congress of Pharmacists (3; 1980; Chisinau): Abstracts of reports. Chisinau, 1980, p. 79-80.

76. Kozmin, V.D. Using the Rebinder effect to intensify the production of pharmaceutical suspensions / V.D. Kozmin // Everything is growing. Congress of Pharmacists (4; 1981; Voronezh): Materials. Voronezh, 1981.-S 276-277.
77. Kozmin, V.D. Theoretical foundations for the selection of surfactants for the stabilization of pharmaceutical suspensions / V.D. Kozmin // All-Union. Congress of Pharmacists (3; 1980; Chisinau): Abstracts. report Chisinau, 1980 .-- P. 81.
78. Gayevy, M.D. Pharmacotherapy with the basics of clinical pharmacology: Textbook. for pupils pharmacy. Universities / Gayevy M.D., Galenko-Yaroshevsky P.A., Petrov V.I. Volgograd, 1996. - S. 204 - 207; 214216.
79. Dick, I.G. Hydrodynamic model of acceleration of sedimentation of fine particles in bidispersed suspension / I.G. Dick, L.L. Minkov, T. Neesse // Thermal physics and aeromechanics. 2001. - T. 8, No. 1.- S. 283 - 294.
80. Gorbakov, V.V. Comparative characteristics of antisecretory drugs of various groups according to the data of daily pH-monitoring /
81. B.V. Gorbakov, Yu.S. Makarov, T.V. Golochalova // Lech. doctor 2001. -№ 5 - 6. - S. 11.
82. State Pharmacopoeia of the USSR. -X ed. - M .: Medicine, 1968. —1. P. 1079.
83. State Pharmacopoeia of the USSR: Vyts. 1. General methods of analysis / Ministry of Health of the USSR. 11th ed., Add. - M: Medicine, 1987 .-- 336 p.
84. State Pharmacopoeia of the USSR: Issue 2. General methods of analysis / Ministry of Health of the USSR. -11th ed., Add. M: Medicine, 19S7. - 398 p.
85. Gradus, L.Ya. Manual for analysis of variance by microscopy / L.Ya. Degree - M., 1979 .-- 28 p.
86. Grakovskaya L.K. Suspension as a dosage form / L.K. Grakovskaya, G.B. Barsheva // Vseros. Congress of Pharmacists (4; 1981; Voronezh): Materials. Voronezh, 1981 .-- S. 272 - 274.
87. Grigoriev P.Ya., Diagnosis and treatment of diseases of the digestive system / Grigoriev P.Ya., Yakovenko E.GT. -M .: Medicine, 1996.508 p.

88. Grigoriev P.Ya., Gastroenterology reference guide / Grigoriev P.Ya., Yakovenko A.V. -M., 1997.410 p.
89. Holbreich, JI.C. Chitin and chitosan: structure, properties, application / L.S. Holbraich // Soros Education. zhurn. 2001. - T. 7, No. 7. -S. 51-56.
90. Semyonova A.V., Korsunskaya M.V. Content analysis of the media: problems and application experience / Ed. V. A. Mansurov. - M .: Institute of Sociology RAS, 2010 .-- 324 p. - ISBN 978-5-89697-188-7.
91. http: // studfiles.net/preview/6761345/page:42/ - ...
92.http; // pharmacopoeia 2020. 11.august, Eurasian unions.
93. *Milliken, William; Milliken, Douglas (1994). Race Car Vehicle Dynamics. SAE International. pp. 617–620. ISBN 978-1560915263.*
*94."BMW Technology Guide : Self-levelling suspension". BMW. Retrieved 16 May 2018*
*95.."Suspension Basics 4 - Torsion Bar Springs". Initial Dave. Archived from the original on 10 May 2010. Retrieved 29 January 2015.*
96. Salomons, W. & Groot, A. J. de., 1978. Pollution history of trace elements in sediments, as affected by the Rhine river. In: Krumbein, W. E. (Ed.) Environmental Biogeochemistry and Geomicrobiology, Vol. I: The Aquatic Environment. Ann Arbor Science Publishers Inc., Ann Arbor, Michigan. 394 pp.
97. Sly, P. G., 1969. Bottom sediment sampling. Proc. 12th Conf. Great Lakes Res., International Association of Great Lakes Research, pp. 883-898. Sly, P. G., 1981. Equipmentand techniques for offshore survey and site investigations. Can. Geotechn. J. 18: 230-249. Smith, J. D., Nicholson,
98.R. A. & Moore, P. J., 1973. Mercury in sediments from the Thames estuary. Environ. Pollut. 4: 153-157. Turekian, K. K. & Wedepohl, K. H., 1961. Distribution of the elements in some major units of the earth's crust. Bull. Geol. Soc. Am. 72: 175-191.
99.Vinogradov, A. P., 1962. Average contents of chemical elements in the principal igneous rocks of the Earth's crust. Geokhimiya 7: 555-571. (As cited by Parker,

R. L., 1967. Data of Geochemistry. D. Composition of the Earth's Crust. Prof. Paper U.S. Geol. Surv., 440-D. 19 pp.).

100. Wedepohl, K. H., 1960- Spurenanalytische Untersuchungen an Tiefseetonen aus dem Atlantik. Geochim. cosmochim. Acta 18:200-231. Word, J. Q., 1976. Biological comparison' of grab sampling devices. In: 1976 Annual Report. Coastal Water Research Project, El Segundo, Calif., pp. 189-194.

101. S.J. SontagThe medical management of reflux esophagitis. Role of antacids and acid inhibition Gastroenterol. Clin. North Am., 19 (3) (1990), pp. 683-712

102. D.L. Decktor, M. Robinson, P.N. Maton, F.L. Lanza, S. Gottlieb

103. Effects of aluminum⁄magnesium hydroxide and calcium carbonate on esophageal and gastric pH in subjects with heartburn

104. Am. J. Ther., 2 (1995), pp. 546-552,

105. R. Sweis, M. Fox The global burden of gastro-oesophageal reflux disease: more than just heartburn and regurgitation Lancet Gastroenterol. Hepatol., 5 (6) (2020), pp. 519-521,

106. S. Nasim, M.A. Mustufa, S.I.H. Zaidi, M.T. Khan, A. Wajid

107. Liquid antacids: a comparative study on palatability and cost effectiveness Pak. J. Med. Sci., 28 (2012), pp. 183-186

108. M.E. Temple, M.C. Nahata Comparative palatability of 22 liquid antacids Aliment. Pharmacol. Ther., 14 (2000), pp. 421-425,

109. S. Jacob, A. Shirwaikar, S. Anoop, R. Khaled, M. Imtiaz, A. Nair Acid neutralization capacity and cost-effectiveness of antacids sold in various retail pharmacies in the United Arab Emirates Hamdan Med. J., 9 (2) (2016), pp. 137-146,

110. C.D.K. Amengor, O.F.W. Akuffo, J. Kwaning, A.H. Iddrisu, A. Ohemen g, D.A. Acheampomaa, P. Gyapong Acid neutralizing capacity of selected antacid suspensions available in the Ghanaian market Asian J. Res. Med. Pharm. Sci., 9 (2020), pp. 10-15,

111. I. Ayensu, S.O. Bekoe, J.K. Adu, A.A. Brobbey, E. Appiah Evaluation of acid neutralizing and buffering capacities of selected antacids in Ghana Sci. African., 8 (2020)World Health Organization. Quality Assurance and Safety of Medicines. Tool for visual inspection of medicines. Available at:

112. B. Schiavetti, E. Wynendaele, V. Melotte, J. Van der Elst, B. De Spiegeleer, R. Ravinetto A simplified checklist for the visual inspection of finished pharmaceutical products: a way to empower frontline health workers in the fight against poor-quality medicines J. Pharm. Policy Pract., 13 (9) (2020)

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