BASIC PRINCIPLES FOR THE CLASSIFICATION OF MEDICINAL FORMS

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Scientifically justified classification of medicinal forms is of great theoretical and practical significance for the development of pharmacy. The classification of medicinal forms can be carried out according to various signatures such as the consistency, aggregation state, administration pathway, production technology, degree of dispersion, delivery form, kind of production, and generalized classification. The advantages and disadvantages of each principle of classification are considered.

Key words: classification, medicinal forms, consistency, aggregation state, administration pathway, production technology, degree of dispersion, delivery form, kind of production

The insufficiently developed classification of medicinal forms (MF) was certain to stimulate scientific interest in this problem. A scientifically justified classification is of great practical and theoretical significance for the development of any branch of science. The history of scientific development shows that the creation of similar classifications fostered the discovery of the most important laws of nature.

The variety of MF requires them to be classified. Classification helps to characterize individual phenomena and facts depending on the assignment to one group or another and to determine the optimum method for preparing the preparation. It simplifies the study of the material and, furthermore, enables yet unknown or unstudied phenomena and objects to be predicted [1, 2].

The significance of classification for MF technology, like for other scientific disciplines, is difficult to formulate unambiguously. A scientifically justified classification enables several problems to be resolved professionally:

To systematize prepared MF;

To develop production technology for MF, to select the required preparation conditions and optimum type of technology. For example, MF suspensions (see below) are classified separately according to dispersology. Depending on the properties of the dispersed phase and dispersion medium, preparation of suspensions in some instances is carried out without a stabilizer (syspensions of hydrophilic compounds); in others (supensions of hydrophobic compounds), with a requisite stabilizer;

To justify the MF packaging methods;

To justify storage methods and predict the behavior of the preparation upon storage;

To create in the pharmacy and recommend to the patient or medical hospital personnel the required conditions and optimum length of storage;

To develop methods for investigating the quaity and to ensure its required control at all stages of production technology;

To predict the nature of the pharmacological effect (rate, completeness of release and assimilation of drugs from the MF);

And to develop plans for organizing MF production [1, 2].

Classification signatures are the basis of any classification. Signatures on the basis of which MF that are at first glance unrelated can be combined, combining signatures, must first be identified. Then, signatures on the basis of which a single MF can be differentiated from the others, separating or distinguishing signatures, must be identified. Classification signatures should be selected with a thorough understanding of the objects to be classified. Thus, the identification of important signatures reveals intrinsic peculiarities of the objects to be classified. External properties must be completely evaluated in classifying MF because they are a consequence of the manifestation of intrinsic properties.

MF can be classified from various angles because they are characterized by a certain set of properties. Therefore, a single array of MF can be placed in different sequences depending on what properties are taken as the classification signatures. This does not at all mean that a certain classification signature cannot be used for the classification. This is possible if it is used not isolated from the others but in combination with them. It is necessary to recall that separate signatures cannot be artificially combined. Only those signatures that reveal the intrinsic content of the objects to be classified can be combined.

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An analysis of the literature indicates that the classification of MF can be based on MF classification signatures such as consistency, aggregate state, administration pathway into the patient organism, production technology of the given MF, degree of dispersion, delivery form, kind of production, and generalized classification [1 – 3].

All currently known MF classifications have serious disadvantages because there is no sequential separation of MF into classes, subclasses, groups, subgroups, etc. in any of them. Several fundamental comments must be made without a detailed review of all classifications.

Classification according to aggregate state. The earliest classification of MF was that according to aggregate state that was proposed by Academician Yu. K. Trapp (1814 – 1908). According to this classification, all MF are subdivided into four groups: solid, liquid, soft, and gaseous. The MF aggregate state is due mainly to the dispersion medium and to the dispersed phase only for allopathic powders and homeopathic triturations [1, 2].

Solid MF include collections, powders, homeopathic triturations, tablets, pills, suppositories, granules, and microgranules. Liquids include mixtures, drops including homeopathic, homeopathic alcohols, oils, matrix tinctures, aqueous extracts, lotions, rinses, baths, and injection and infusion preparations. Soft MF are ointments, pastes, homeopathic liniments, patches, and suppositories (at body temperature). Gaseous MF comprise gases, vapors (sprayed liquids), and aerosols.

A disadvantage of this classification is first of all that the meaning of "aggregate state" is not entirely correct. Some confusion of aggregate state and consistency is possible.

The title "according to aggregate state" in this classification evolved historically and persists until now. A substance can exist in three states depending on the distance (ordering) between its particles and on their mobility (and interactions). These are the solid, liquid, and gaseous states. Namely these states are called aggregate ones [3].

This classification includes MF that are usually called soft. The aggregate state soft is not usually separated [3]. However, the term soft matter is found in the foreign literature [4]. The term soft matter is still unusual for nonspecialists and is already entrenched in modern science, like the meaning of solid state. Soft material refers usually to partially disordered (unordered) media that are easily damaged by changes caused by comparatively weak external forces. They can be various materials from plastics and surfacants such as soap to liquid crystals used in electronic devices and complicated biological systems such as cellular membranes. From the viewpoint of MF technology, they can be colloidal mixtures of a single compound with others in various phases, for example, gels, films, ointments, etc. Soft material is becoming the subject of broad research by biologists, chemists, physicists, pharmacists, etc. Therefore, it can be said that criticism of soft MF from the viewpoint of classification according to aggregate state is unfounded [1, 2, 4].

Classification according to aggregate state with all its issues allows the following problems to be addressed:

To systematize originally MF and to establish the fraction of an actual group in the whole amount of preparation, for example, liquid MF in the current inventory of a pharmacy is 60%; solid, 20%; soft, 20%;

To produce an original concept of the type of production technology because the ability to add a certain MF to a preparation is related to the aggregate state;

To select the packaging suitable for this aggregate state (suppositories, powders packaged in "paper capsules" as a single-dose paper package used in the pharmacy; ointments and pills in glass bottles; liquid mixtures in glass vials etc.);

To predict to a certain extent the rate of onset of the pharmacological effect. Liquid MF as a rule act faster than solid. Solutions for injection are characterized by absolute biological availability [1].

However, classification according to aggregate state has the following disadvantages:

A single MF can be included in different groups depending on the physical properties of adjuvants. For example, suppositories prepared from cocoa butter are soft MF; in a polyethyleneoxide base, solid;

Special requirements imposed on MF depending on the application area are not considered. For example, powders placed on a wound surface or designed for injection (after dissolution in an appropriate solvent) should be prepared under aseptic conditions and be sterile in contrast with powders intended for internal application, in which the microbiological purity is regulated;

Complete information on the nature of the production technology cannot be obtained. For example, liquid MF can have different production technology steps depending on the dispersion medium used, the properties of the drug, and the administration pathway of the preparation.

Classification as a function of administration pathway and application. This classification was first proposed by V. A. Tikhomirov and is currently being improved. All MF are divided into two large groups depending on the administration pathway, enteral [administered through the gastrointestinal (GI) tract] and parenteral (administered by-passing the GI tract) [2].

The enteral pathway of administering a preparation includes two methods.

Peroral (*per os*) is the most common, simple, and convenient pathway for administering preparations. Both solid and liquid MF are conveniently taken through the mouth. They are relatively slowly assimilated in the stomach and small intestine and are observed in the blood stream at least 30 min after administration.

The assimilation time of the drug depends on the functional state of the mucous, the GI tract contents, the pH of the medium, and other factors. Therefore, this administration pathway cannot be used to give immediate care. The peroral administration pathway is ineffective for certain compounds such as those that are decomposed either in the acidic environment of the stomach (pancreatin, insulin, antibiotics) or by enzymes in the intestines.

A modification of the peroral pathway is sublingual administration (under the tongue) for local and general treatment. Drugs are rather quickly assimilated through the mucous of the oral cavity and enter the general blood circulation while avoiding the barriers of the GI tract and liver. Sub-

lingual compounds are those with high activity such as sex hormones, validol, and nitroglycerine, all at low doses.

The rectal (from Latin rectus, direct) administration pathway through the colon (*per rectum*) is used for both local and general treatment. The rectal administration pathway is convenient in pediatrics and geriatrics in addition to unconscious patients. Assimilation of the drug begins after 7 – 10 min through the lower and middle hemorroidal veins, the pancreatic vein, and the lower genital vein. More than 75% of the drug enters immediately the general circulation, avoiding the liver. Compounds are not affected by enzymes of the alimentary tract. Doses of compounds from lists A and B should be observed and checked for the rectal pathway [1, 2, 5].

The parenteral (from Latin par entheron, past the intestine) administration pathway comprises a large variety of methods [1, 2].

Preparations of various MF (powders, poultices, ointments, pastes, liniments, patches, etc.) are placed on the skin. The drug action can be both local and general (resorptive or reflectory) because the skin contains a significant number of nerve endings.

Compounds that are soluble in fat (phenol, camphor) and liquids that dissolve the fat film of the epidermis (ethanol, CHCl3, ether) are assimilated well through the skin. Gases and volatile substances (iodine) pass easily through the skin. The assimilating ability of skin increases with mechanical damage, hyperemia, and maceration. Aqueous solutions are almost not assimilated through undamaged skin. Compounds in emulsions penetrate well through the skin. Drugs can be administered using ionophoresis, a method based on the action of a constant electric field, for example, solutions of electrolytes, alkaloids, or antibiotics, through undamaged skin.

Placement of medicinal agents on mucous membranes (eye, nose, ear, urethral, vaginal MF) is widely used. Mucous membranes have good assimilating capability owing to the presence of many capillaries. Mucous membranes do not have a fatty adlayer and assimilate well aqueous solutions of drugs.

Urethral and vaginal forms were widely used not only locally but also for drugs directed at organs of the small pelvis [2, 5].

Inhalation forms (from Latin, inhalare, to breathe) administer drugs through the respiratory pathway and include gases (oxygen, nitrous oxide, ammonia) and volatile liquids (ether, $CHCl_3$). Slightly volatile liquids can be administered using inhalers. The extent of drug assimilation in this instance is explained by the enormous surface of the lung alveoli (50 – 80 m^2) and the abundant network of blood vessels. The drugs have quick action because they pass directly into the circulation [1].

Parenteral MF include injectables administered using a syringe. Drugs quickly enter the blood and exert an effect after 1 – 2 min and earlier. Injectable forms are needed for giving immediate care. They are convenient for unconscious patients and for administering drugs that are destroyed in the GI tract.

Special requirements are placed on injectable MF. These include sterility, apyrogenicity, absence of mechanical inclusions, etc. [1, 5].

Classification depending on the method of administration has technical significance because MF are given certain requirements, the observation of which should be guaranteed by the production technology, depending of this. This classification allows the following problems to be resolved:

To resolve the question of the need to check doses of compounds in lists A and B. Doses of preparations for the enteral administration pathway are always checked;

To predict the rate of onset of the pharmacological effect and the nature of assimilation. Injected MF have an absolute biological availability;

To provide the necessary preparation conditions (aseptic for preparing injectable solutions, MF for newborns, for placement on wounds and burns);

To select the type of control (absence of pyrogens in infusable liquids; particle size in powders, etc.); to formulate the preparation according to the administration method. For example, to apply labels “External, Internal, Eye drops,” etc.

Depending on the pathway and method of administration, labels with the appropriate conventional color are used [1].

Division of MF into external and internal in certain instances may appear dubious, for example, assignment of rectal, inhalation, sublingual, and certain other MF as external [5]. Classification of MF according to administration method has several other disadvantages:

Various MF that differ sharply by form, structure, and technology are included in the same group. For example, powders, pills, and mixtures can be used internally. However, drops can be designed for internal use, placement on eye mucous membranes, administration into natural or pathological cavities, etc.;

The nature of the production technology is in general not specified;

Certain modern MF are difficult to include definitively in a certain group (sublingual, implantable, magnetically directed, etc.).

This classification of MF is meaningful mainly for physicians. The administration pathway determines the strength and rate of onset of the drug effect [1].

Classification based on structure of dispersed systems (dispersological). Dispersological classification should be viewed as the most appropriate and important one for the technician because it is based on a definable signature, the nature of the structure of dispersed systems [1, 2].

Two basic problems are solved by preparing all complicated preparations. The drug is dispersed optimally and distributed evenly in the carrier mass (volume). These issues must be solved in all instances regardless of the aggregate state, administration pathway, and method of preparation use.

Physicochemical systems in which a ground compound is distributed in another are called dispersed (from Latin dispersius, scattered, dispersed). The dispersed compound makes up the dispersed phase; the carrier, the continuous dispersion medium. Therefore, all complicated MF are various

dispersed systems. MF technology is a variety of dispersology, the study of dispersed systems that was developed by Academician P. A. Rebinder and colleagues. The dispersological classification of MF proposed by N. A. Aleksandrov and developed by A. S. Prozorovskii considers all MF taking into account the following factors. The presence or absence of a bond between particles of the dispersed system; the aggregate state of the dispersion medium; the nature of the dispersed phase partitioning [3].

Two main opposite groups are distinguished according to the modern classification depending on the presence or absence of a bond between particles of the dispersed system. These are freely dispersed and bound-dispersed systems.

Particles of the dispersed phase either do not interact in freely dispersed systems or interact weakly. Therefore, particles can freely shift relative to each other under the influence of thermal motion or the force of gravity. Freely dispersed systems are aqueous solutions, solutions in viscous and volatile solvents, mixtures, drops for external and internal application, rinses, lotions, emulsions, suspensions, aqueous extracts, liniments, etc. Bound-dispersed systems consist of fine solid particles that touch each other and are bonded by molecular forces to form three-dimensional networks and frameworks in the dispersion medium. Particles of the phase do not migrate and can only exhibit vibrational movement. As a rule, bound-dispersed MF are porous solids that are produced by compression or gluing of powders (granules, pressed tablets, micropellets). This subgroup includes solid microcrystalline alloys consisting of solid crystallites welded to each other (cocoa butter, solid paraffin, glycerine suppositories, gel suppositories) [1, 2].

Bound-dispersed systems can contain dispersion medium or be free of it. This causes a number of problems.

The fact that the term “dispersed” is used for a system consisting of a dispersed phase, a combination of partitioned particles and a continuous dispersion medium, in which these particles exist in a suspended state, suggests that the dispersological classification of MF also has several disadvantages and assumptions, like the other classifications. For example, powders are according to this classification very often considered free thoroughly dispersed systems with a solid dispersed phase and without a dispersion medium, despite the presence of a gaseous (air) dispersion medium, on the basis that it is not added additionally by the technician but is the natural environment. Powders are not formally aerogels, i.e., systems prepared by coagulation of aerosols with a solid dispersed phase although powders are in fact prepared by dispersion.

Dispersed systems are divided according to the aforementioned criteria into several subgroups depending on the presence or absence of a dispersion medium and its aggregate state. There are those without a dispersion medium, with liquid, viscous-plastic, solid, gaseous dispersion media, and systems with a foam structure [1].

Particles of a solid are not distributed in the carrier mass in systems without a dispersion medium (based on the assumption that there is no dispersion medium from a technical viewpoint because it is not added during preparation of the MF). These systems are divided according to dispersion into crudely dispersed (collections) and finely dispersed (powders, homeopathic triturations). They are produced by mechanical grinding and stirring. The main properties are a high specific surface area; a corresponding reserve of surface free energy; increased adsorptivity; and adherence to the law of gravity.

Systems with a liquid dispersion medium include all liquid MF [1]. The following types of dispersed systems are identified according to the dispersion of the phase and the nature of the bond to the dispersion medium.

Solutions in various solvents, homogeneous systems with the maximum granulation of the dispersed phase (ionic and molecular, 1 – 2 nm) that is bonded to the solvent through the formation of solvated complexes without an interface between phases, true solutions of low-molecular-weight and high-molecular-weight compounds;

Sols or colloidal solutions (micellar partitioning). The particle cross sections are less than 100 μm. An interface is found between the phases (ultramicroheterogeneous systems);

Suspensions, microheterogeneous systems with a solid dispersed phase and a liquid dispersion medium. The interface between phases can be seen with the unaided eye. Particle sizes are less than 0.2 – 100 μm. These dimensions in pharmaceutical suspensions are in the range 30 – 50 μm;

Emusions, dispersed systems consisting of two liquids that are soluble or slightly soluble in each other, a phase and a medium, liquids that are mutually immiscible. The drop size of the liquid phase is less than 20 μm;

Combined systems. In this instance the production technology results in the dissolution or peptization, suspension, or emulsion of the dispersed phase in dispersion media of different viscosity.

Systems with a visco-plastic dispersion medium have an aggregate state intermediate between a liquid and solid. Depending on the dispersion and aggregate state of the phase, these can be solutions, sols, suspensions, emulsions, and combined systems. They can be formless systems with the appearance of a continuous common mass (ointments, pastes) that cannot take a geometric shape or formed systems (suppositories, spheres, rods) that are prepared by pouring into special forms or manually (rolling) [1, 2, 5].

Spumoids are dispersed systems with a foam structure (from Latin spuma, foam) in which the liquid or visco-elastic medium is a continuous thin film. Typical spumoids are highly concentrated suspensions and emulsions and pills [1].

The dispersed phase in systems with a solid dispersion medium can be dissolved or solid or emulsified particles. Poured or pressed spheres and medical pencils prepared from fatty materials or solid synthetic bases (for example, polyethyleneoxides) are used most often.

Systems with a gaseous dispersion medium include gas solutions, clouds, and smoke for inhalation, smoking, and aerosols.

The partitioned dispersed phase in any of the aforementioned dispersion media can be homogeneous, heterogeneous, and combined dispersed systems.

Homogeneous (molecular and ionic dispersion) systems are true solutions of low-molecular-weight compounds, homeopathic dilutions, and true solutions of high-molecular-weight compounds.

Heterogeneous systems include ultraheterogeneous (colloidal solutions); microheterogeneous; suspensions (solid particles of the dispersed phase); and emulsions (liquid particles of the dispersed phase). Combined systems can involve various types of dispersed systems (homeopathic matrix tinctures, tinctures and decoctions, ointments) [1, 3].

The nature of the production technology, i.e., the essence and sequence of processing operations, determines the classification of MF based on the structure of the dispersion systems more than for the other types of classification. It can solve the following problems:

To select the optimum type of technology (grinding, with preparation of powders, suspensions; dissolution, with preparation of true and collodial solutions; stabilization, for preparation of suspensions, emulsions, etc.);

To predict the stability of MF during storage of both homogeneous (highly stable) and heterogeneous (unstable) systems;

To evaluate the quality of preparations, for example, solutions should be transparent (homogeneous systems); suspensions, evenly cloudy (microheterogeneous systems), suspensions, suspended liniments; powders, a definite particle size.

Classification according to features (nature) of dosage. Dosed (powders, pills, suppositories, tablets, solutions for injection in ampuls, films) and undosed (mixtures, powders, liniments, certain homeopathic MF, etc.) forms are distinguished according to this classification. This classification can take a different approach to checking doses of compounds in lists A and B and can resolve questions about the nature of the packaging, select the appropriate packaging, take a different approach to quality control (checking the number of doses, deviations in the mass of doses, etc.) [1, 2].

A disadvantage of the classification is that a single group includes MF of different structure or aggregate state, with different production technology and administration pathway. A single MF can be dosed and undosed. For example, injectable MF can be dosed, solutions for injection, and undosed, solutions for infusion [5]. MF belonging to the undosed group can transition to the group of dosed MF (for example, ointments in single-dose packaging).

Classification of MF depending on patient age. This classification proposed division of MF into the following groups: pediatric, patients up to 14 years old (a special group includes MF and preparations for newborns up to 1 month old); middle-aged patients (from 14 to 60 years old); and geriatric (patients over 60 years old).

The differences consist mainly in the prescribed doses of compounds in lists A and B and others and the permissibility of administering auxiliary compounds of one type or other taking into account anatomic-morphological and physiological peculiarities of the patient. For example, preservatives, stabilizers of physicochemical processes, (with a rare exception) are not included in preparations for newborns. The preparation conditions are strictly regulated for this group. All MF for newborns and children up to one year old regardless of the method of use should be prepared in pharmacies under aseptic conditions. A disadvantage of this classification is the singularity of the classification signature, age [1, 2, 5].

Classification according to nature (features) of effect on the organism. According to this classification MF are divided into two groups. These are primarily local (for example, on skin or mucous membrane) and general action on the organism (resorptive and/or reflectory). This subdivision in several instances is very arbitrary. Depending on the adjuvants used and the nature of the production technology, local or general action on the organism can be provided. Use of various adjuvants can direct drugs to target organs, regulate release, prolong action, and activate assimilation through a high release rate of drugs from the MF and/or rapid resorption (assimilation). The main disadvantage of the classification, which is due to production operations for preparing the MF, is that, as a rule, several processing schemes are used to prepare the MF. This causes corresponding difficulties in the assignment to one group of MF or another. The main disadvantage of a generalized classification is the noncritical relation to the used particular classifications.

Despite the rather large number of MF classifications at present, there unfortunately is no universal MF classification. Any of the existing classifications has its positive sides and disadvantages. Each separate MF classification, based on its own approaches and principles, helps to solve various problems. Success of one classification or another is determined by how successfully the classification signatures are selected. The classification algorithm is considered good if the use of it allows the optimum or subsystem very similar to it to be determined for a number of steps that is significantly less than for the full set.

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