RESEARCH ARTICLE

Pharmacopoeian Aspects of Suspensions Preparation in Pharmacy Conditions

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Abstract

Aim: This study aims to analyze the classification, nomenclature, advantages of modern auxiliary substances, and prospects of using them in development of extemporal suspensions; to evaluate the pharmacopoeian requirements to extemporal suspensions preparation. **Materials and Methods**: In the work, the retrospective, logical, and analytical research methods have been used to analyze the data of special literature and regulatory framework. **Results and Discussion**: Based on the data of modern scientific literature, the requirement for extemporal suspensions is outlined. The detailed analysis of modern auxiliary substances (suspending agents, stabilizers, etc.) most often used and approaches to the choice of them in the process of suspensions development is given. **Conclusion**: Approaches to selecting of auxiliary substances have been considered. The monitoring of pharmacopoeian requirements demonstrated that the chemists require the detailed information about technologies, auxiliary substances, picking, and package/storage conditions for extemporal forms.

Key words: Extemporal medicines, stability, stabilizers, suspending agents, suspensions, technology

INTRODUCTION

Pharmacy used oral liquids are developed in the form of solutions, suspensions, and emulsions, depending on the nature of medical substance, its solubility and stability. The additional substances are solvents, stabilizers, viscosity modifiers, preservatives, sweeteners, coloring agents, and aromatizers. Herewith, there is an important problem of medicaments compatibility to the additional substances. Their right choice guarantees the obtaining of stable, effective liquid oral usage drug form with proper taste. It is vital to know that substance degrading mechanism, some of its physical and chemical features to reach that purpose such as solubility and pH stability. To rapidly define this compatibility, we need to cover the pH stability profile with the same of pH solubility.[1,2]

Suspensions are heterogeneous systems containing two phases. The external phase, which is also referred to as the continuous phase or dispersion medium, is generally a liquid (e.g., liquid suspensions) or semisolid (e.g., gels), and the internal or dispersed phase is made up of particulate matter, which is practically insoluble in the external phase. The most pharmaceutical suspensions consist of an aqueous dispersion medium.[1,3,4]

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.[1,5]

At present, many drug formulations are available as suspensions. Some therapeutic classes of drug formulations are mentioned below:

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- Oral antacid suspensions;
- Oral antibacterial suspensions;
- Oral analgesic suspensions;
- Oral antifungal suspension;
- Dry antibiotic powders for oral suspensions preparation;
- Topical lotions, etc.

In an ideal suspension formulation, insoluble particles should be uniformly dispersed. However, on standing, the solid particles in suspensions get separated from the liquid as sediments. Regardless of the amount of sedimentation, a well-formulated suspension should redisperse uniformly in the continuous phase, on moderate shaking, for a sufficient period of time. This allows the withdrawal of the correct amount of medication with minimal dose variation. The rate of settling can be decreased using viscosity improving agents, and the ease of redispersibility can be controlled using flocculating agents. Products that are too viscous, however, may not be easy to remove from the container and may be too difficult to transfer to the site of application. Furthermore, the drug diffusion process is also expected to be hindered by high viscosity. It, therefore, presents a challenge to the formulator to find a suitable viscosity-imparting agent and a flocculating agent, which, when used at appropriate concentrations, allow the optimum rate of sedimentation and easy redispersion in a quality product. Suspended particles should also be small and uniform in size to provide a smooth and elegant product that is free from a gritty texture.[6-9]

One of the most important factors, influencing the pharmaceutical suspensions development, is the picking of proper suspending agent. It gives the viscosity to the heterogenic system and slower the particles sedimentation improves the rheological properties and needs to provide the chemical compatibility with other additional substances alongside the pH stability. They form a hydrophilic coverage round the solid particles and thus provide their wetting.[10]

The suspending agents - high molecular compounds (HMCs) or surface-active substances (SASs) are classified as derivatives of cellulose, natural (gelatin, tragacanth, alginates, and bentonite) and synthetic (carboxypolymethylene and polyvinylpyrrolidone iodine).[11-14] They can often be combined with each other. The Table 1 gives the list of suspending agents, most of all used in oral liquids, and their features.[2] We give the used concentration and corresponding feature (e.g., ion charge, water dispersibility, and pH range). The pharmacy suspensions making requires the special attention.

One of the characteristic features of suspensions is their ability to settle. That is why the stability is one of the important requirements to them, there are the sedimentary and aggregational suspension stability. Sedimentary stability prevents the particles from sedimentation due to their size. Suspensions stability will be the more; the less is the radius of dispersive phase. Hence, the grinding process is the important technological operation at suspensions preparing, which able to disperse the solid drug particles as thin, as possible. This is succeeded by its precise grinding in the pounder in a dry form and then with adding some liquid. The dry substances grinding dispersion grade must be near 50 μm, and when they are grinded in the presence of some water, the particles size at 0.1…5 μm.[1,15]

Suspension stability depends on the ratio of dispersed particles in dispersive phase with dispersive environment. The denser the dispersive phase is the faster the particles settle; when the density is lower, they surf faster. When the densities are near the equal index, the suspension is the most stable.

The suspensions sedimentation obtains two different variants. At first, the particles settle separately, without connection with each other. The settlement is slower. This dispersive system is classified as aggregatively stable. However, we can

Table 1: Stability pH range and concentrations of most commonly used suspending agents

Suspending agent	Stability pH range	Concentrations used as suspending agent, %
Sodium alginate	4–10	1–5
MC	3–11	1–2
Hydroxyethyl cellulose	2–12	1–2
Hydroxypropyl cellulose	6–8	1–2
Hydroxypropyl methylcellulose	3–11	1–2
CMC	7–9	1–2
Sodium CMC	5–10	0.1–5.0
Microcrystallic cellulose	1–11	0.6–1.5
Tragacanth	4–8	1–5
Xanthan gum	3–12	0.05–0.5
Bentonite	pH>6.0	0.5–5.0
Caraginate	6–10	0.5–1.0
Guar gum	4–10.5	1–5
Silicon colloid dioxide	0–7.5	2–4

MC: Methylcellulose, CMC: Carboxymethyl cellulose

have another accident, when the solid suspension particles coagulate under the action of molecular gravity forces and sediment in the whole flakes form. Those systems are aggregatively unstable.

Thus stability of suspensions depends onepy properties of medicinal substances contained in them, mainly when they have a hydrophilic or hydrophobic surface.

The hydrophilic substances suspensions are more stable because their particles are moisturized by dispersive environment and get provided with a hydrate shell, preventing from the lesser particles aggregation into the bigger. However, the hydrophobic ones are not protected by such shell, so they are easily glued, forming the flakes, which fast sediment. When the flakes are formed at suspensions coagulation and are badly moisturized by water, they surf. At this time, the flocculation is spectated on the water surface.[3,4,16,17]

To increase the hydrophobic substances suspensions, they need to get lyophilized, i. e., added with the hydrophilic colloid (stabilizer).[18,19]

Theoretical proof of extemporal suspensions technology based on the rules of powder grinding and hydrophobic suspensions stabilization.[20,21] The powders grinding is made according to State Pharmacopoeia of Ukraine (SPU) 2.0 "Pharmacy powders." The need in liquid addition is explained by substance solidity lowering, besides that, the moisturizers penetrate the little cracks of solid particles, which form at the substances grinding and perform the wedging pressure, which acts oppositely to the Laplace pressure. The microcracks widen and the further grinding is succeeded. Hence, the more the substance is grinded; the stable and effective suspension is alongside its dosage precision. The maximal substances dispersion effect is seen in the liquid environment with the addition of 0.4–0.6 ml liquid (or half) per 1.0 g solid substance.[1]

To prepare the suspensions with hydrophobic substances, the stabilizers (HMSs and SASs) are added. The hydrophobe/stabilizer ratio depends on the substance hydrophobicity index and stabilizer hydrophiliating properties. The substances with acute hydrophobic features are menthol, camphora, timol, etc.; the weak hydrophobic properties substances are terpin hydrate, phenyl salycilate, sulphanilamides, etc. The stabilizer quantity for extemporal suspensions is calculated with Table 2.

The stabilizers hydrophilization features are considered to manifest in water presence. That is why they get previously mixed with stabilizer, when the hydrophobe-containing suspensions are prepared, and further, the water gets added in quantity, equal to the half-sum of hydrophobe and stabilizer.[1,20]

In general, the hydrophilizing properties of HMCs or SASs are defined, using different experimental methods. Bondarenko with coauthors offered the definition method, based on powder immersion into the SAS solution.[22,23] According to given method, to define the SAS concentration, required for the hydrophobic substances moisturizing, the medical substance powder gets grinded to 40 μm, dried to the constant mass, and put into the exiccator over the dried calcium chloride. Then, 0.02 g substance is put on 1 cm^2 solution surface, containing the different concentrations of SASs in a 30 ml glass with 45 μm diameter.[1,24]

The time of powder immersion into the SAS solution is fixed by a chronometer. Basing on the obtained data, the graphic of powder immersion time ratio to the SAS concentration is built. The perpendicular is put from the point of tangentals to the abscisses axe. The crossing point of perpendicular and abscisses axe points out the SAS concentration required for the powders moisturizing. The investigation results give the conclusion about the needed SAS concentration, providing the hydrophilization of drug. This quantity must be optimal. The optimal quantity hiring causes the gelling process. When there is not enough HMCs, the astabilizing can commence because of no enough HMC parts for full weighed particles coverage and protection.[18,19]

This method sets the moisturizing parameters and critical surface tension for the diverse medical substances. The Table 3 gives a critical concentration of drug powders polysorbate-80 (tween-80) moisturizing. It is needed to consider, that tweens and spens are incompatible with salicylates, peroxybenzoic acid derivatives, phenols, etc.

The suspension particles can also be stabilized by adding the electrolytes, which create the defined sign and gross zeta potential. The zeta potential in suspensions is explained just like the micelle core charging in hydrophobic sol: The ion adsorption from solution and dissociation/hydrolysis of solid phase surficial layer.[24-26]

It is considered that electrolytes stabilize the suspensions only in the defined concentrations. When the concentration is higher the stabilizing electrolyte action transfers to coagulating.

The dispersive phase of suspensions can sediment on the container bottom while storing. The sedimentation can also cause the sediment sintering and solidification with resulting difficulty of resuspension at mixing. To prevent those problems, we need to add the viscosity increases to suspension.[3,26]

It is important to shake the suspension well before the usage to equally distribute the solid substance in the solvent, providing the precise and proper dosage.

There are different works by many native and foreign authors dedicated to the investigation of different theoretical and practical aspects of suspensions preparation.[27-29]

Table 2: Stabilizer quantity per 1.0 g hydrophobic substance

Stabilizer quantity, g	1.0 g substance	
	Acutely manifested hydrophobic properties	Weakly manifested hydrophobic properties
Apricot gum	0.5	0.25
Gelatose	1.0	0.5
5% MC solution	2.0	1.0
Polysorbate-80 (Tween-80)	0.2	0.1

MC: Methylcellulose

Table 3: Critical concentration of medicines moisturizing with polysorbate-80

Medicine	Polysorbate-80 concentration, %
Salazodimethoxin	0.05
Diucifone	0.07
Sulfamethazine	0.1
Etazole	0.1
Salazopyridazine	0.1
Xeroform	1.3

Yu Krylov *et al.* studied the native and foreign normative document requirements offered the dispersion norms in pharmaceutical suspensions: The most particles must be <10 μm and not bigger than 40 μm.[30]

There were also studied the intensifying questions of pharmaceutical suspensions preparation, using the Rebinder effect and also the surficial tension as a mean of stabilizers quantity definition in a drug. The surface tension isotherms helped to define the SAS quantity to hydrophylize the surface of hydrophobic substances.[27] Some investigations are dedicated to the studying of medicaments dispersity index in pharmaceutical suspensions and their different properties, stabilization questions.[28,31-33] The given works helped the intensive development and involvement of suspensions into medical practice.

Today, almost all countries of the world have SPs issued by government bodies and reflect the achievements of pharmaceutical science.

The SP is a collection of medical standards and provides the basic principles of the preparation of medical forms. It has a legislative character, binding on all medical institutions and enterprises in the country involved in the preparation, storage, control, and usage of medicines.[34]

The European Pharmacopoeia is the current intergovernmental pharmacopoeial standard, which defines the requirements for technology and quality control of medicines. However, in current editions, it does not contain separate monographs on extemporal drugs.

The literature depicted the suspensions technology in world pharmacopoeias. Hrakovska and Barysheva first developed the pharmacopoeia article project for pharmaceutical suspensions, which contained a diversity of norms for semi-finished suspensions, mostly antibiotics, which need to have the water added before the use.[32] Those drugs, according to the US Pharmacopoeia, are released with "for oral suspension preparation" label.

While talking about the suspension quality pharmacopoeial aspects, we need to outpoint that Union of Soviet Socialist Republics (USSR) SP had no article that regulates of suspension quality, but the different author articles spoke about the definition of particles homogeneity and size. The first suspensions article was added to the XI part of USSR SP, issue 2.[35,36]

The SPU 1.2 (2008) has the following articles about suspensions: "Liquid topical drugs" (p. 330) and "Liquid oral drugs" (p. 332), dedicated to solutions, emulsions, and suspensions.[37]

The International, British, Indian, and United SP contain the general article about suspensions giving the general requirements to the given medicinal form.

American Pharmacopoeia gives the article No 1151 "suspensions," which informs and explains every question, useful and required for daily pharmaceutical work during the extemporal suspensions manufacturing.[38] It contains the general part, highlighting the questions about suspensions definition, their preparation requirements and rules of packing, storage, and labeling in chemists laboratory conditions. It also has four parts ("oral suspensions," "topical suspensions," "otic suspensions, and" "ophthalmic suspensions").

The oral suspensions are defined as liquid medicinal forms, composed of solid insoluble particles, dispersed in a liquid phase, containing the proper aromatizes, and allowed for oral usage. The oral suspensions category contains the drugs marked as "Milk" and "Magma."

The "milk" term is sometimes used for the suspensions with water solution solvent, assigned for the oral usage (e.g., Milk of Magnesia).

The "magma" term is often used for the description of non-organic substance suspensions like the clay in water, where we can spectate the tendency for strong hydratation and solid substance aggregation, causing the gel consistency ant thixotropic rheology (e.g., Bentonite Magma).

The external usage suspensions are defined as liquid drug forms, containing the solid disperse phase, distributed in liquid environment, and assigned for skin application. This drug group contains the lotions.

The "lotion" term is used to classify a lot of actual suspensions and emulsions used for skin application (e.g., calamine topical suspension).

The otic suspensions are defined as the drugs, containing the micronized powder and assigned for intra-aural application.

Besides, there are 35 monographies about the individual extemporal suspension prescriptions, norming them contain, technology, quality of marking and package alongside the release rules. For example, the suspensions of allopurinol, captopril, methasone, chinidine sulfate, terbinafine chloride, tetracycline hydrochloride, etc.

The question of some extemporal prescriptions standardization in Ukraine is resolved by issuing the methodical recommendations, confirmed by the Ministry of Health of Ukraine order No 398 from 01.07.2015. They contain the systematized extemporal recipes, used in modern pharmaceutical practice, the list of medicaments with the definition of their physicochemical, pharmacological features, incompatibilities, and the grounded way of their addition to the drug form contain. There are given the contain, technology, storage, and usage conditions for every drug mean.[39]

By analyzing the pharmacopoeian requirements, we need to admit that USSR SP article "suspensions" in XI issue and SPU 1.2. (2008) preferably calculate the requirements for industrial manufacturing. It is very difficult to prepare and evaluate the quality of extemporal suspensions, using those articles requirements.

The chemists require the detailed information about the technologies, additional substances picking, and package/storage conditions for extemporal medicinal forms. Basing on the theoretical and experimental investigations generalization, we offer to include the project of "Pharmaceutical Suspensions" article into the SPU to use in pharmaceutical practice.[40]

SUMMARY

1. Based on the review, suspensions stabilization has been highlighted;
2. Approaches to selecting of suspending agent and stabilizers have been defined;
3. The main pharmacopoeian aspects of suspensions preparation in pharmacy condition are described;
4. The project of "Pharmaceutical Suspensions" article into the SPU to use in pharmaceutical practice has been proposed.

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