Comparative characteristics of gel bases for semisolid dosage forms

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Abstract. The article provides an overview of modern data on the main gel bases used in the technology of semisolid dosage forms. The main classes of gelling substances are characterized. According to data, the choice of excipient must be justified from the point of view of the physicochemical properties of the active substance, and depends on the place of application of the gel.
Keywords: *technology of semisolid dosage forms, gels, physicochemical properties.*

1 Introduction

Gels are semisolid dosage forms which are used for local or transdermal delivery of active ingredients, or emollient or/and protective action. Gels include, in addition to gelling agents of natural or synthetic origin, preservatives, stabilizers and emulsifiers, one or more active ingredients. Gelling agents can act as stabilizers for such dispersed systems as suspensions or emulsions. As a rule, gels have a viscous consistency, they are homogeneous, transparent, fluid, elastic and plastic [1-4].

A characteristic feature of gels as a dosage form is the light application, the duration of retention and long-term contact with the surface and, as a result, a high therapeutic effect.
The most important component of gels is the gel base. Modern pharmaceutical manufacturing uses a wide variety of semisolid dosage form bases. This is due to differences in the physicochemical properties of the active components that make up the semisolid dosage form compositions. Today, there are several classifications of bases for semisolid dosage forms. The classification of bases for semisolid dosage form according to sources of receipt is presented in table 1.

2 Classification of gels

The bases for semisolid dosage form are classified according to their chemical composition: e.g. glycerol ethers, hydrocarbons, polysaccharides, inorganic compounds, etc. The disadvantage of these classification is that it is not related with the manufacturing

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technology of dosage form. The most rational classification, which fully reflects the production technology of semisolid dosage form, is the classification of the bases according to the ability to interact with water. Such a detailed classification clearly characterizes the properties of the bases and contributes to its rational and competent selection, depending on the properties of the dosage form (table 2).

Table 1. Classification of bases for semisolid dosage form, compiled according to literature [5, 6]

Parametres		**Bases**
Sources	Natural and modified natural	Fats, fatty oils, petrolatum, liquid paraffin, lanolin, beeswax, bentonite, sitosterol, starch, gelatin, collagen, chitosan, agarose, hyaluronic acid, carrageenan, hydrogenated fats, cellulose derivatives, sodium alginate.
	Synthetic	Cellulose derivatives
		Polymers based on poly (meth) acrylic acid: Carbopol, polycarbophil, polyacrylic acid, polyacrylates, copolymer of acrylic acid and PEG, copolymer of methyl vinyl ether and methacrylic acid, poly-2-hydroxyethyl methacrylate, copolymer of acrylic acid and ethylhexyl acrylate, polymerization of acrylic acid and ethylhexyl acrylate, polymerization of acrylic acid and ethylhexyl acrylate, polyisohexylcyanoacrylate.
		Others: Poly-N-2-hydroxypropyl methacrylamide, polyoxyethylene, PVA, PVP, thiolated polymers, light-crosslinked copolymer of acrylic acid derivative with allyl pentaerythritol ester (NH4-SACAP), silicone fluids.

Table 2. Classification of bases for semisolid dosage form according to interaction with water [5,6]

No.	**Type**		**Base**
1	Lipophilic	Fatty	Pork fat, cocoa butter, sunflower, peanut, olive, peach, almond, apricot oil, hydro fat, mixed fat
		Hydrocarbon	Vaseline, paraffin, liquid paraffin, petrolatum, ceresin
		Silicone	Esilon-aerosil base, esilon-4, esilon-5, cyclomethicone, liquid silicone, dimethiconol
		Polyethylene and polypropylene	Plastibase
2	Hydrophilic	Protein	Gelatin, collagen
		Polysaccharides	Cellulose ethers
		Inorganic substances	Bentonite clays, aerosils
		Synthetic	PEO and PEG, PVA, PVP, polyacrylamide, acrylic acid copolymers
		Oligoesters	Esters of polyhydric alcohols (glycerin, sorbitol, diethylene glycol, etc.) with polybasic acids (tartaric, citric, succinic, etc.)
		Others	Regencur, phytosterol, chitosan, xanthan gum, guar gum, alginates, carrageenates, etc.
3	Diphilous	Absorption	Anhydrous alloys of hydrophilic bases with emulsifiers, anhydrous alloys of lipophilic bases with emulsifiers, alloys of petroleum jelly with anhydrous lanolin
		Emulsion	Oil / water, water / oil

The selection of the gel base in the technology of dental gels is a particularly important aspect, the bioavailability of the medicinal product depends on this fact. To increase bioavailability, the phenomenon of mucoadhesion occupies a special place. Mucoadhesion is the ability of an object to stay on the surface of the mucous membrane or skin for a long time. Therefore, dental gels used for the treatment of periodontal diseases are mucradhesive dosage forms. Attachment to mucous membranes leads to an increase in the concentration of active ingredients of the drug at the site of application. It has been established that the addition of certain polymers, for example, gums, to the composition of the drug, lengthens the residence time of the drug on the mucosal surface and increases the effectiveness of the drug [7]. For these purposes, mucoadhesive polymers are used (table 3).

Table 3. Classification of mucoadhesive polymers [6]

No.	Basic of classification	Class	Examples
1	Solubility in water	Water soluble	Carbopol, HEC, HPC, HPMC, Na-CMC, sodium alginate, chitosan (aqueous solutions of acids)
		Water insoluble	Ethyl cellulose, polycarbophil
2	Charge	Cationic	Aminodextran, dimethylaminoethyldextran, chitosan, quaternized chitosan
		Anionic	Chitosan-EDTA, carbopol, polycarbophil, pectin, sodium alginate, Na-CMC, CMC
		Uncharged	Hydroxyethylated starch, HPC, PEG, PVA, PVP
3	Possible mechanism for the formation of bioadhesive bonds	Covalent	Cyanoacrylate
		Hydrogen bonds	Acrylates, carbopol, polycarbophil, PVA
		Electrostatic interactions	Chitosan

The most promising for use on mucous membranes are hydrophilic bases. They contain substances or their combinations that can dissolve in water or form stable systems with the formation of gels.

In the scientific literature, the following hydrophilic bases are most fully described: starch gels, gelatin-glycerin gels, collagen gels, polyethylene glycol (polyethylene oxide) gels, cellulose ether gels, gels of lightly cross-linked acrylic polymers (carbopol, arespol), gels of clay minerals, polyvinylpyrrolidone gels, polyvinyl alcohol and hyaluronic acid acid gels.

Starch gels are colorless, transparent, homogeneous, viscous masses, easily distributed over mucous membranes. Previously, they were used for the preparation of eye ointments. Low stability due to syneresis and the impossibility of long-term storage was the main reason for the sharp decline in the use of this base in pharmacy practice.

In the end of 20th century starch-glycerin gel was used, also known as glycerin ointment. The composition includes 7 parts of starch, 7 parts of water and 93 parts of glycerin. It spreads easily on the mucosal surface, due to the presence of glycerin, the gel is resistant to the effects of microorganisms, but during storage it is prone to syneresis [8,9].

It is known that scientists are currently conducting research on the preparation of starch copolymers giving natural starch properties that are not inherent in it under normal conditions. The main advantage of this discovery is that, compared to synthetic copolymers, their biodegradability is higher. On its basis, absorbents and superabsorbents, flocculants (substances that violate the stability of a colloidal solution with particles of impurities), as well as gels and hydrogels are obtained. These compounds are non-toxic and completely decompose in the body [10-12].

Gelatin gels are light yellow, transparent, homogeneous viscous liquids. They are used in the form of gelatin-glycerin bases, which contain 1-3% gelatin, 10-30% glycerin and 70-80%

water. They are used to obtain protective ointments - the so-called skin adhesives, which solidify on the skin in the form of a strong elastic film.

Collagen gels. Collagen is a natural biopolymer that is a fibrillary protein of animal connective tissue. It is obtained from certain areas of the skin in the form of a pasty mass or solution. Collagen is used to produce films containing drugs for various purposes. Collagen is very promising for ointments, as it is a prolonger and regulates the flow of drugs through the skin. Collagen preparations reduce the inflammatory response, activate reparative processes and shorten the time of wound healing, which is confirmed by the successful use of collagens in burn therapy. In terms of the completeness of the release of medicinal substances, the base is several times superior to the mixture of petroleum jelly with lanolin (90:10) [11].

Polyethylene oxide (PEO) based gels: polyethylene oxide is produced by ethylene oxide polymerization or ethylene glycol polycondensation. Depending on the molecular weight, PEO can be conditionally divided into low-molecular and high-molecular compounds with different properties [3]. According to the physical properties, PEO can be divided into three groups (Table 4). PEO bases have a pH close to that of the skin and a viscosity that makes it possible to obtain stable gels [13].

Table 4. Physicochemical properties of polyethylene oxides of various molecular weights [13]

Properties	**PEO - 300**	**PEO - 400**	**PEO - 600**	**PEO - 1500**	**PEO - 2000**	**PEO - 4000**	**PEO - 6000**
Appearance	Transparent colorless or slightly yellow liquid		White dense mass		Waxy white flakes		
Average molecular weightn	270-330	380-440	550-650	1400-1600	1800-2200	3500-4500	5400-6600
pH (5% aqueous solution)	5,0-7,5	5,0-7,5	5,0-7,5	5,0-7,0	5,0-7,0	5,0-7,0	5,0-7,0
Water, %, no more	1,0	1,0	1,0	1,0	1,0	1,0	1,0
Color of 25% aqueous solution, Hazen units, no more	20	20	20	35	35	35	30
Kinematic viscosity at (40.0 ± 0.3) ° C, mm² / sec, within	30-34	39-45	59-66	-	-	-	-
Kinematic viscosity at (99 ± 0.3) ° C, mm² / sec, within	-	-	9-13	27-35	38-45	100-160	260-340
Crystallization temperature, 0C, within	Not regulated	18-25	43-48	48-53	50-55	53-57	

A combined base of 60 parts of PEO-400, 40 parts of PEO-4000 has found application in pharmaceutical technology. This base is incompatible with phenols, silver salts, mercury, iodides, tannin, resorcinol. Due to their dehydrating properties, the bases dehydrate the

mucous membranes, causing irritation and a burning sensation. The advantage of these bases is that they are soluble in water and other polar solvents, so they are easily washed off from the skin and linen. The bases are resistant to light, temperature and moisture; insensitive to the introduction of electrolytes and changes in pH. They have a weak bactericidal effect due to the presence of primary hydroxyl groups in the molecule and therefore do not undergo microbial contamination.

Rare crosslinked acrylic polymers (RCAP) gels are produced both under the brands Arespol, mArss, Carbopol (Carbomer). According to their chemical structure, they are high molecular weight polymers of acrylic acid, chemically cross-linked with polyalkenyl alcohols or divinyl glycol. The process of obtaining carbopols consists in the polymerization of acrylic acid in various solvents. Depending on the type of substituent, carbopols are classified into 5 groups:

1. Carbopol homopolymer - a polymer of acrylic acid, cross-linked with allyl sucrose or allyl pentaerythrol;

2. Carbopol polymer is a polymer of acrylic acid and C10-C30 alkyl acrylate, cross-linked with allyl pentaerythrol;

3. Carbopol interpolymer is a carbomer homopolymer or copolymer containing a polyethylene glycol-ester copolymer block with a long chain alkyl substituent;

4. Pemulen polymer is an acrylic acid polymer modified with long-chain acrylate chains (C10-30), cross-linked with allyl pentaerythrol;

5. Noveon AA-1 Polycarbophil is a polymer of acrylic acid cross-linked with divinyl glycol [8,9,14].

Gels based on RCAP have a number of advantages over other gelling agents: when applied to the skin, they form the thinnest smooth films that are well distributed over mucous membranes and skin surfaces, providing a prolonged effect of drugs, more fully and evenly release medicinal substances, thus ensuring pharmaceutical availability [15]. In addition, they are not subject to metabolism, since they have a high molecular weight.

According to its physical properties, it is a white, light, fluffy, hygroscopic powder. In this regard, special conditions are imposed for storing the excipient - in a tightly sealed container, in a dry place. With regard to chemical stability, carbopols are stable when stored under normal conditions. In the course of experimental studies, it was found that during 5 years of storage, significant changes in the stability indicators of the substance were not observed. The powder itself is insoluble in water, but has the ability to swell in water and in some polar solvents.

Carbopol polymer acts as a gelling agent in semisolid dosage forms manufacturing. Various brands of Carbopol are known in the pharmaceutical industry. For example, Carbopol 934 is highly effective in viscous forms such as viscous gels, highly concentrated emulsions and suspensions and provides high stability. In aqueous media, it has low fluidity, fast recovery. Carbopol 940 - forms transparent gels with water or water-alcohol mixture, has the lowest possible fluidity and is applicable in the form of a spray. Carbopol 980 is the most effective thickener of carbopol polymers, easily dispersed and mixed. Ultrez 10 and 21 carbopols form aqueous dispersions with the following properties: easy to disperse and mix; less prone to lump formation; have a much lower viscosity before neutralization, which makes it easy to pump concentrated dispersions. In appearance, they are flaky powders; the diameter of the fractions is from 2 to 7 microns [16]. It is known that in the production of semisolid dosage forms, this polymer is in low concentrations (0,1 - 3%). This amount is sufficient to form a gel with the required viscosity. For example, in aqueous-alcoholic gels for external use, the average level of carbopol is 0,5 - 3%. At the same time, for oral suspensions, it is sufficient to use 0,1–1% of the excipient [8,9,14].

There is a directly proportional relationship between the concentration and viscosity of a carbopol-based gel. Thus, in order to increase the viscosity of the gel, it is necessary to

increase the concentration of the gelling agent. It is known that the polymers Carbopol 981 NF, 971 PNF and 941 NF give gels with low viscosity.

Of great importance is the fact that the viscosity of carbopol-based gels can be adjusted using the pH changing. It is necessary that the polymer is neutralized by the base, after which it thickens. The maximum viscosity is achieved at a neutral medium pH 6.0 - 7.0.

For systems where the ability to control the pH is excluded, the degree of formulation can be increased by hydrogen bonding with hydroxyl donors of other components. Polyols are used as donors, i.e. polyhydric alcohols (eg glycerin), sugar alcohols (mannitol, sorbitol), nonionic surfactants, polyethylene oxides. Due to their binding to hydrogen groups, a kind of neutralization occurs, as in the regulation of pH. Thus, three parameters affect the final viscosity of a carbopol gel: carbopol concentration, pH, and degree of hydrogen bonding. [9].

Clay mineral gels, also known as bentonites, interact well with water (swell and hold it firmly). There are their sodium forms, which swell when wetted with water, increasing in volume by 15-18 times. Bentonite gels are well distributed on the skin and are chemically indifferent. The ability of bentonite to turn into a gel when added with water makes it possible to use it for the preparation of dry concentrates in the form of powders or tablets. According to the simplest prescriptions, the bentonite base consists of 13-20% of the sodium form of the mineral, 10% of glycerin and 70-77% of water.

Polyvinylpyrrolidone gels. Polyvinylpyrrolidone (povidone) is a colorless, transparent, amorphous, hygroscopic polymer compound in powder form, soluble in water, glycerin, PEO, chloroform, practically insoluble in diethyl ether. Aqueous solutions of polyvinylpyrrolidone change color during long-term storage, and can also be susceptible to microbial contamination, therefore preservatives are introduced into their composition. Polyvinylpyrrolidone is miscible with cellulose derivatives as well as with lightly crosslinked acrylic polymers. It forms soluble complexes with vitamins, antibiotics, tannins, dyes. As bases for semisolid dosage forms, gels are used in a concentration of 3% to 20%. On the basis of PVP gels, an ointment is made for treating wounds, containing an aqueous solution of ethanol, tannin, and cinnamon alcohol. To improve blood circulation and reduce pain, cooling compositions have been proposed, intended for application to tissue and containing turpentine, camphor, menthol, eucalyptus oil, and plant extracts in PVP gels. PVP gels are widely used in cosmetics in the manufacture of creams, masks, and mascara [17].

Polyvinylpyrrolidone gels must be prepared by heating in a water bath. The required amount of gelling agent is thoroughly mixed with water, then placed in a water bath. Heating is completed when the polymer swells, but then vigorous stirring is continued until the mixture has completely cooled. This is necessary for the system to be homogeneous.

Hyaluronic acid gels. Due to its unique physicochemical properties, hyaluronic acid has found application in various fields of medicine: veterinary medicine, cosmetology, periodontology, ophthalmology, arthrology, traumatology, etc. treatment of diseases associated with these tissues. Viscoelastic hyaluronic acid solutions and its gels are used as solid biocompatible “barrier substances” to prevent post-surgical adhesion and excessive scarring [18,19].

Due to its physicochemical properties, such as high viscosity, specific ability to bind water and proteins and form proteoglycan aggregates, hyaluronic acid contributes to the manifestation of numerous functions of connective tissue, which is especially important in the regeneration of periodontal tissues and oral mucosa. Hyaluronic acid can act as an active component with anti-inflammatory and wound-healing properties, and as an excipient, as a gelling agent, which helps to increase the permeability of tissues for the transfer of active components of the dosage form. Hyaluronic acid has a high water-holding capacity: one molecule of hyaluronic acid can bind from 200 to 300 water molecules. In this regard, it is widely used in dentistry. Hyaluronic acid -based preparations used in periodontology are produced in the form of gels, powders, membranes [20-23].

Cellulose ethers are often used as excipients in dental gel technology. They meet all the requirements for excipients and have a number of advantages over other polymers. Cellulose ester gels are viscous, structured, transparent, release drugs well, provide resorption, are biologically harmless, are compatible with many drugs, have no irritating effect, are capable of forming homogeneous mixtures with secretions of mucous membranes, have adsorption properties, absorb well exudates and, thus, clean the treated surface [24].

Cellulose ethers are products of replacement of hydrogen atoms of hydroxyl groups of cellulose with various acyl or alkyl radicals [3]. By their structure, they are odorless and tasteless powders or fibrous masses. In pharmaceutical practice, 3-8% methyl cellulose gels are used (3% gel for the manufacture of eye ointments) and 4-6% Na-carboxy methyl cellulose gels [25]. Cellulose ester gels are viscous, structured, transparent, odorless, well release medicinal substances, provide resorption, and are biologically harmless [14, 26]. The most commonly used cellulose ethers are shown in Table 5.

Table 5. Physical properties of cellulose ether derivatives [16,27,28]

No.	Cellulose ether	Physical properties
1	Methylcellulose	White, yellowish-white powder or granules, hygroscopic after drying, practically insoluble in hot water, acetone, anhydrous ethanol and toluene. It dissolves in cold water gives a colloidal solution
2	Ethyl cellulose	White or yellowish-white powder, or granules, odourless or almost odorless, practically insoluble in water, soluble in methylene chloride and in a mixture of 20 g ethanol and of toluene, slightly soluble in ethyl acetate and in methanol, practically insoluble in glycerine (85%) and in propylene glycol. Solutions may show slight opalescence
3	Sodium carboxymethyl cellulose	White or beige fibrous powder without characteristic odour. It is very soluble in cold and hot water with the formation of colloidal solutions
4	Cellulose acetate	Flaky white or yellowish powder, odourless and tasteless. Soluble in water with the formation of colloidal solutions. Soluble in chloroform, dichloroethane, formic and acetic acids
5	Hydroxypropyl methylcellulose	White or beige dusty powder, odorless and tasteless. Soluble in water and in some organic solvents, for example, in a mixture of ethanol and methylene chloride

From a technological point of view, gels based on cellulose derivatives are quite laborious to manufacture and, depending on the brand, have a number of features (table 6).

Table 6. Features of the technology for obtaining gels on some brands of cellulose derivatives [29-32]

Cellulose ether	Concentration, %	Technology features
Methylcellulose	2-4	Easily and quickly dissolves in water at a temperature of 20-25 ° C
Sodium carboxymethyl cellulose	4-8	Easily and quickly dissolves in water at a temperature of 20-25 ° C
Hydroxyethyl cellulose	4-8	Slowly dissolves in cold water and at a temperature of 20-25 ° C, dissolves better in water at a temperature of 40-50 ° C
Hydroxypropyl methylcellulose	2-10	It is recommended to heat 1/3 of the volume of water to 80 ° C and add the polymer with stirring, stir for about 30 minutes, then add the rest of the water 5-10 ° C

Hydroxypropyl cellulose	5-20	Dissolve slowly in water heated to a temperature of 45-60 ° C until complete dissolution and cooling of the solution to 20-25 ° C
Methylcellulose + Sodium carboxymethyl cellulose	3-7	Easily and quickly dissolves in water at a temperature of 20-25 ° C

3 Conclusion

Thus, there are currently a large number of different groups of substances capable of gelation. The choice of excipient must be justified from the point of view of the physicochemical properties of the active substance, and depends on the place of application of the gel.

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