ORIGINAL ARTICLE

Prospects of Using Synthetic and Semi-Synthetic Gelling Substances in Development of Medicinal and Cosmetic Gels

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Abstract

Aim: The work is to analyze the range, classification, nomenclature, and advantages of modern synthetic and semi-synthetic gelling substances and prospects of using them in developing gels. **Materials and Methods:** We have used retrospective, logical, analytical, marketing, and economic research methods for the analysis of modern synthetic and semi-synthetic gelling substances. **Results and Discussion:** The detailed analysis of modern synthetic and semi-synthetic gelling substances most often used or promising in the development of cosmetics and medicines was carried out. **Conclusions:** The monitoring of gelling substances of semi-synthetic and synthetic origin demonstrated that the range of the accessory substance group allows to develop up-to-date cosmetic and pharmaceutical gels with satisfactory consuming, physicochemical, and rheological characteristics.

Key words: Cosmetic product, gel, gelling substance, medication, semisynthetic gelling substance, synthetic gelling substance

INTRODUCTION

Now gels are the most common product form in various industries. This product form has been of particular demand for developing cosmetics and medicines for the past 15 years. Gels are systems that contain at least two components which consist of dispersed phase, distributed in the dispersion medium. The dispersion medium is liquid. The dispersed phase is gelling substance, polymer chains of which form the cross-linked net and does not have the mobility that exists in the molecules of a thickening agent in high-viscosity solution. The water in such system is physically linked and also loses its mobility.[1,2]

The result is a change in the consistency of the base. The structure and the strength of the gels obtained using different gelling substances may vary considerably.

The main component of gels is gelling substance which, in addition to creating colloidal structures, increase stability, increases the shelf life of ready-to-use products, etc. Nowadays, in the pharmaceutical and cosmetics industry, many gelling substances of different origin are used. Despite wide range of gelling substances nomenclature, developers often use Carbomers (it is explained by a fairly large number of brands with various characteristics) or cellulose derivatives (methylcellulose [MC] or sodium carboxymethylcellulose [CMC]).

However, the number of modern gelling substances of complex nature of significant advantages over carbomer and cellulose derivatives is used abroad.

It should be noted that despite wide range of gelling substances nomenclature, there is no scientific grounding for using the group of these substances in terms of pharmaco-technological, structural and mechanical, and other studies.

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Nowadays, in the world, and in Ukraine as well, the interest to the subject of developing gels for various effect is growing, which determines the importance of better understanding of the nomenclature of modern gelling substances - substances with which gel is made.

So based on the above, the analysis of modern synthetic and semi-synthetic gelling substances most often used or promising in the development of cosmetics and medicines is important and timely.

The aim of the work is to analyze the range, classification, nomenclature, and advantages of modern synthetic and semi-synthetic gelling substances and prospects of using them in developing gels.

MATERIALS AND METHODS

In the work retrospective, logical, analytical – for analyzing data of specialized literature and regulatory framework – as well as marketing and economic research methods have been used to ground the sociomedical practicability, the cost-effectiveness of developing new medications, and cosmetics in the form of gels.

RESULTS AND DISCUSSION

In the pharmaceutical and cosmetics industry, macromolecular substances – acrylic acid copolymers – have been widely used in the development of soft medication forms. Acrylic acid copolymers provide high gelling characteristics at low concentrations (1%). Moreover, structural and mechanical properties of medications with acrylic gelling substances (structural viscosity, thixotropic character, etc.) remain stable during long-term storage. There were developed dermatological, ophthalmic, nasal, and other medicines based on acrylic copolymers. In the cosmetics industry, these gelling substances are essential in developing gels, emulsions (o/w) and suspension creams, shampoos, and serums.[3-5]

Carbomers (Carbopol, BP: Carbomers, PhEur: Carbomera, USP: Carbomer) by "Lubrizol" company are the most popular representatives of this group of macromolecular compounds. When producing gels, emulsions and suspensions, and different brands of carbomers are used: 940, 980, 934R, 971R, 974R, 1342, 1382, 5984, 2984, Ultrez 10, Ultrez 21, ETD 2001, ETD 2020, etc.

In oral, gels brands 934R, 971R, and 974R are used. In their synthesis, less toxic solvents - ethyl acetate and mixture of ethyl acetate with cyclohexane - are used.

Currently, two mechanisms of gelling are used the result of which is a complete unwinding of the polymer molecules. The first one is carried out with a neutralizing agent. This mechanism is well represented in scientific literature. As neutralizer for Carbopols sodium or potassium hydroxide (10% solution) or trometamol are most often used. The most important structural viscosity index is obtained when pH range is from 5 to 10.

The other gelling mechanism involves using hydroxyl - donor (without a neutralizing agent) as a result when creating hydrogen bonds gelling occurs. In most cases, the gelling process occurs within 10 min (heating to 60°C accelerates the process). To gel Carbomers glycols (propylene glycol, glycerin) are often used.

Among these Carbopols, polymer brand Ultrez 10 (permitted by USP to be used in pharmacy), and Ultrez 21 stand out. These gelling substances form gel system in 5 min without stirring, and viscosity indexes are significantly higher than other brands of Carbopols. They are especially attractive to the cosmetic industry - gels obtained have a nice look (shiny transparent base).[6-8]

It is known that gels based on Carbopol are sensitive to electrolytes; ETD 2020 Carbopol brand is used for thickening gels with electrolytes, anionic, and amphoteric surfactants. Gels with ETD 2001 Carbopol brand have better mechanical stability. Carbopol concentration of 0.4-1, 0% is recommended.[9,10]

As a result of the polymerization technologies development, the nomenclature of the acrylate monomers, crosslinking, and modifying agents expands every year. Nowadays, in development of cosmetic preparations complex polymers are increasingly used.

Poloxamers (Pluronic, BP: Poloxamers, PhEur: Poloxamera, USP: Poloxamer) are a group of copolymer composed of one hydrophobic group of polypropylene oxide (PPO) located among hydrophilic groups of polyethylene oxide (PEO). The basic formula poloxamers are the following one: $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_a$. The pH value (2.5% of aqueous solution) is from 5.0 to 7.4. The most common poloxamer brands are presented in Table 1. For example, 188 poloxamer brand can be written as $(PEO)_{75}$-$(PPO)_{30}$-$(PEO)_{75}$.

Taken in high concentrations (20%), poloxamers form thermo processing gel. When heated, the gelling process is faster. This is connected with amphiphilic nature of poloxamers:

Table 1: Major poloxamer brands

Poloxamer brand	a	b	MW
124	12	20	2090-2360
188	80	27	7680-9510
237	64	37	6840-8830
338	141	44	12,700-17,400
407	101	56	9840-14,600

Micelle-like combined zones are formed at the room or higher temperature. The combined zones contain large amounts of micelle-like structures which are likely to form the viscous liquid crystal phase. Poloxamers also form gel systems in the water-alcohol solution.

Poloxamer gels are used to make "artificial skin" that is required to treat third-degree burns. They are non-toxic, accelerate healing, control the loss of water, heat, and electrolytes and provide cleaning the content of wounds.

As poloxamer is thermally transformed, poloxamer solution is applied to the damaged tissue, and the gel is formed directly on the wound due to the body temperature. These gels are easily washed off with cold water. Poloksamer gels resemble mucus and are optically transparent, so they are used to develop ophthalmic medications. This polymer is also used as an emulsifier in creams, ointments; solubilizer and stabilizer as elixirs, syrups, and as a base for suppositories. This gelling substance is used while developing dermatologic drugs, such as benzoyl peroxide for preventing and treating acne. The concentration from 0.3% to 50% is used.

"Salcare SC 80" (stearate-10 allyl ether/acrylic copolymer, Siba) complex acrylic copolymer, gelling is carried out due to the presence of long chain hydrophobic groups.

Swelling of the gelling substance occurs due to the formation of micelle after neutralizing with organic or inorganic alkaline base.

In acidic medium, there is no significant in turgescence. When neutralizing, the electric repulsion between anionic groups leads to the polymer chain unwinding, which leads to immediate in turgescence. Advantages: Dispersion is of milky color, so when neutralizing agent is added to the water-polymer mixture, a clear gel base is instantly created. The recommended concentration of polymer is up to 5%.

"RapiThix A-60" (sodium polyacrylate/hydrogenated polydecene/trideceth, ISP). This polymer is the emollient-based solution. It does not require prior dispersion, or prior in turgescence or heating. It can be added for viscosity correction after the formation and cooling of emulsion. It instantly forms cream gels at room temperature when added directly to water. It is compatible with many cosmetic ingredients.[11-13]

The recommended concentration of this complex polymer is up to 5%. "Aristoflex AVC" (a mixture of acrylamidopropylsulfonic acid and vinyl pyrrolidone, Clariant Surfactants, Switzerland) is a complex gelling substance of a new generation. It does not contain carbohydrates and aromatic solvents. It is used as gelling substance in aqueous systems and thickening agent in emulsions of "o/w" class (provides stability even in the absence of additional emulsifier). The stabilizing effect of "Aristoflex AVC" is explained by the structure of the polymer: Gel coats droplets or solids (e.g., pigments).

"Aristoflex AVC" softens the dense texture of cream and provides the effect of mini skin tightening. Emulsions of "Aristoflex AVC" is perfectly applied to the skin and quickly absorbed. Systems of gels with this gelling substance are characterized by good sensory properties, without stickiness. Hydrogels transparency depends on the concentration of "Aristoflex AVC" used in a formulation. "Aristoflex AVC" concentration of 1% or higher ensures transparent gels. Adding hydrophilic non-aqueous solvent from 5% improves hydrogels transparency. The most transparent gels are obtained while using purified or demineralized water. Aqueous-alcoholic transparent gels can be obtained when ethanol at a concentration of more than 50% is added. "Aristoflex AVC" has good compatibility with other polar organic solvents (ethanol, acetone) and is resistant to ultraviolet (UV) radiation. The manufacturer recommends preparing hydrogels as follows: Aqueous phase is added to the powder "Aristoflex AVC" while stirring slowly. When preparing the water-alcohol base, the first aqueous gel is prepared, and then alcohol is added to it. Preferably, anchor mixer is used which moves slowly to minimize "trapping" in air bubbles. "Aristoflex AVC," like other acrylic acid copolymers is sensitive to electrolytes, so it is not suitable for foam-washing formulations that include large amounts of salt. "Aristoflex AVC" gelling substance is recommended to use in a wide range of pH: 4.0-9.0.[5,14,15]

"Aristoflex AVC" is a copolymer, which due to its hydrophobic linkers is used as an effective combining agent. In addition, due to the hydrophilic sulfo groups the polymer interacts with biologically active substances formulations and prolongs their action retaining them on the skin surface longer.

In combination with hyaluronic acid and plant extracts, the polymer ensures deep and efficient cleaning of skin, toning, and waste removal and affects the intensity and duration of BAS effect. Therefore, it is recommended to use "Aristoflex AVC" in products for aging skin, as well as for treating blepharitis and demodicosis. Recommended amount of "Aristoflex AVC" is 0.5-1.5%.[16,17]

Semisynthetic gelling substances for aqueous medium include cellulose simple ethers. They are characterized by different degrees of polymerization and substitution. Their advantages include physiological indifference, stability in a wide range of pH and temperatures.

In the cosmetic and pharmaceutical industry, while producing gels, creams, etc., the following polymers are often used: Sodium CMC (sodium CMC, BP: Carmellose sodium, PhEur: Carmellosum natricum, USP: Carboxymethylcellulose sodium), MC (BP, USP: Methylcellulose, PhEur: Methylcellulosum) and hydroxypropylcellulose (HPC, BP, USP: Hydroxyethylcellulose [HEC], PhEur: Hydroxyethylcellulosum), hidroksypropyltselyuloza (HPC, USP NF: Low-substituted Hydroxypropyl-cellulose.[18-20]

Gels on water-soluble cellulose ethers are prepared with prior soaking in cold water. To increase the speed of gelling, polymer hydrophilic non-aqueous solvent (glycerin) powder pre-dispersing is recommended. Unlike acrylic gels, the bases obtained do not have 100% transparency, their color varies from light yellow to colorless. Cellulose derivatives are widely used in the development of ophthalmic (artificial tears), dermatological preparations. They are especially popular for covering burned tissues (minimize water loss and are easily removed). It is known that sodium-CMC as carrier improves healing of diabetic ulcers.

Based on hydroxymethyl cellulose, a wide range of gels-keratolytics with salicylic, benzoic acid is represented. While producing tablets, these cellulose derivatives are used as filming agents, disintegrants, and as prolongators of active substances in eye drops and injection solutions.[21,22]

In cosmetology, HEC is also used as viscosity regulators in toothpastes, gels for peeling with glycolic acid (pH 2-3), and for depilation (pH 11-12). The recommended concentration of these polymers is from 0.5% to 5%. Nowadays, modified gelling substances are increasingly used while developing preparations of soft medication forms. The main advantage of these products is their rapid dispersion in cold water and stability of the products based on them in a wide temperature range.

In cosmetology, most effective modified gelling substances are the ones by "National Starch" company.

"Structure XL" gelling substance (INCI name: Hydroxypropyl starch phosphate) is a natural substance obtained from corn starch. "AMAZE XT" gelling substance (INCI name: Dehydroxanthan Gum) is also a natural substance obtained from xanthan.

"Structure XL" and "AMAZE XT" are supplied as powder obtained by the unique technology of drying. This method of drying allows to structure water with minimal mixing and dust content. These gelling substances provide long-term stability while freezing and thawing. They also have satisfactory rheological properties, resistance to shear, pH, and temperature.

In connection with the physical and chemical processing mentioned above, "Structure XL" and "AMAZE XT" are easily dispersed in water at any temperature from 5 to 80°C. These modified products do not require additional screening or mixing with any solvent - gel base is immediately formed while adding gelling material to the water. Gelling powder can do without heat processing - it completely dissolves in cold water. At the same time, they are emulsion stabilizers (cold emulsification process), coprocessing agents, rheological modifiers, and aesthetic amplifiers. With "structure XL" and "AMAZE XT" a number of products can be obtained – from gaseous emulsion to thick creams of hot or cold processing. Cold processing takes only some time required for preparation of traditional emulsions.[23-25]

These gelling substances are compatible with a wide range of active and auxiliary substances, such as chemical and physical UV filters, vitamins, plant extracts, α- and β-hydroxy acids, dihydroxyacetone, mono- and divalent salts, flavours and coloring pigment. These gelling substances can be added at any time during the production process. They can even be added at the end to regulate structural viscosity during the process, if necessary. "Structure XL" and "Amaze" aqueous dispersions are stable at concentration of at least 1% (at lower concentration starch will sedimentate to the bottom in aqueous medium).

Inorganic gelling substances, such as aluminum hydrochloride and bentonite clays. Aluminum hydrochloride forms two-phase gel, which consists of a grid of particles distributed in liquid. It is combined with many additives including glycerin, saccharin, etc. The stability of gel increases in the presence of high-molecular alcohols, such as mannitol and sorbitol.

Aluminum hydrochloride gels do not have soothing properties; they are mostly used as oral antacids. Bentonite and hektonite clays consist mainly of hydrated aluminum and magnesium silicates, respectively. Bentonites are notable for their ability to turgesce; one gram can absorb up to 11 ml of water. Magnesium aluminosilicates are used the most often, one of the main representatives of them is bentonite. The main part of bentonite is montmorillonite; also it contains ions of magnesium, calcium, sodium, iron, etc. It belongs to the group of hydrated aluminosilicate and has a three-layer structure. Pharmacy and cosmetology use aluminosilicate free from iron, white or beige. Homogeneous bases are formed by adding bentonite to water in parts (from 5% concentration). Bentonites turgesce in water to form thixotropic gel. To reduce the in turgescence period, it is recommended to use water heated to 80-90°C.

Laponite clay also belongs to the bentonites, but it is synthetic thickening agent. Like bentonite, laponite turgesces in water; to form gel, 2% concentration is required. The laponites do not contain dirt present in natural clays, but to form gel microstructure in aqueous solution electrolytes must be added.

In the pharmaceutical industry, clays are used mainly as thickening agents. Trietanolamine bentonite forms also have emulsifying properties. The ability of these substances to turgesce is used in the technology of tablets, granules, etc.

In cosmetology, this group is used in masks as an active adsorbing component to remove fat, toxins and support hydrolipidic skin film. Because of its high adsorbing capacity, it is recommended only for the care of oily skin. Thus, the analysis of gelling substances of semi- and synthetic

origin allows developing medicinal and cosmetic gels with the satisfactory consumer, physicochemical, rheological characteristics. We have analyzed the dynamics of registered medications in the form of gels by Ukrainian manufacturers.

The Ukrainian manufacturers offer 73% of trade names of medications in the form of gels, which are represented by the following manufacturers: TOV "Effect," "Ozdorovchy biotechnology," "Aromat," "Kalina" concern, "Magiya trav," MNPO "Biocon," "Kosmedfarm," etc.

The dynamics of registered medications in the form of gels according to the price lists of the "Pharmacy" weekly publication is presented in Figure 1.

According to the data from all the groups of products in the form of gels, as of January 2013 at the domestic wholesale market there were 286 offers, in January 2014 there were 380 offers, in January 2015 there were 408 ones, and in January 2016 there were 380 offers from distributors, i.e., for the period from 2013 to 2016 the number of registered medications almost did not changed.

Consequently, most gels were registered in 2014, and in 2015 and 2016 there was registered the same number of preparations in the form of gels.

CONCLUSIONS

1. The analysis of the literature on the nomenclature and characteristics of gelling substances of semi- and synthetic origin has shown that the range of these substances is quite wide. It was pointed out that while developing preparations of soft product forms, including gels, gelling substance and its concentration as the main excipient should be carefully chosen considering the properties of other active substances and excipients, which enter into the composition of the product, and the required rheological, technological and other parameters as well.
2. It has been found out that at Ukrainian market medicinal and cosmetic products, based on gelling substances of various origins are popular. It has been proved that convenient product form for certain medications, - dermatological, dental, anti-inflammatory and wound-healing in particular - is gel because it provides optimal therapeutic properties of active substances, including dissolving, inflammatory, reparative and diverting activity.
3. Basing on the monitoring of gelling substances of semi- and synthetic origin, it has been found that the range of this group of excipients allows to develop up-to-date cosmetic, pharmaceutical gels with the satisfactory consumer, physicochemical, rheological characteristics and to include active substances with any defined parameters (pH, temperature, etc.).

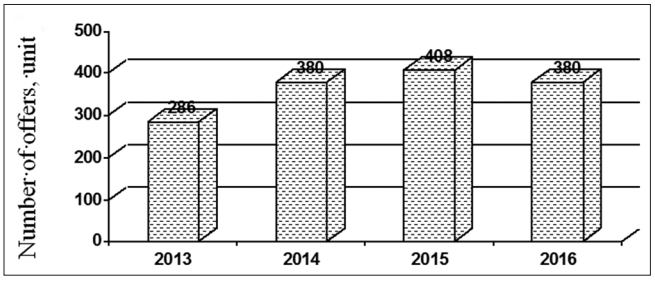

Figure 1: Histogram of the dynamics of the registered medications in the form of gels

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