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Educational guide to
"INDUSTRIAL DRUG TECHNOLOGY. MODERN PERSPECTIVE TECHNOLOGIES IN PRODUCTION SOFT PHARMACEUTICAL FORMS"

(for independent work)

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According to the content of the Drug Technology program, this manual presents the basic theoretical questions required to complete the course and also tests items to check the assimilation of educational material by students.
The publication is recommended for the students of pharmaceutical faculties also for medical high school students.

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INTRODUCTION

Human health depends on the availability of safe, effective, and affordable medicines. The choice of the dosage form, the method of its introduction into the body is an important task of pharmacotherapy. The correctly selected dosage form is the key to the success of treatment, which is associated with the biopharmaceutical properties of the drug, the patient's feelings, and the characteristics of his body. Therefore, the pharmaceutical industry faces the task of increasing the range and improving the quality of finished medicines.

Currently, an important problem in pharmaceutical technology is the prolongation of the duration of action of drugs. Recently, several advances have been made in the development of new drug delivery methods. Along with the creation of new dosage forms and drugs, new technologies and equipment are being developed all over the world

The aim of the discipline "Drugs technology" (industrial technology) is giving to students theoretical knowledge about trends in pharmaceutical production development.

This discipline includes five lectures (10 hours), twenty practical lessons (40 hours), and eighty hours of independent work of students.

This manual consists of **fivetopics**. Upon termination of each unit to students are offered the test for self-checking knowledge. The test includes "Krok-2" tests questions. To each question, there are 5 variants of answers from which correct is only 1. If the student has answered correctly on 80% of questions, the material is acquired well, 80% - it is good, 90% - is excellent. If there are fewer than seven right answers, it is recommended to work the text of the unit repeatedly.

The glossary of terms which meet in the given unit with the explanation of their value and questions which are taken out on seminar also is resulted.

MODERN PROSPECTIVE TECHNOLOGIES IN PRODUCTION SOFT PHARMACEUTICAL FORMS

СУЧАСНІ ПЕРСПЕКТИВНІ ТЕХНОЛОГІЇ У ВИРОБНИЦТВІ М'ЯКИХ ЛІКАРСЬКИХ ФОРМ

Pharmaceutical semi-solid preparations may be defined as topical products intended for application to the skin or accessible mucous membranes to provide localized and sometimes systemic effects at the site of application. In general, semi-solid dosage forms are complex formulations having complex structural elements. They are often composed of two phases (oil and water), one of which is a continuous (external) phase and the other a dispersed (internal) phase. The active ingredient is often dissolved in one or both phases, thus creating a three-phase system. The physical properties of the dosage form depend on various factors, including the size, of the dispersed particles, the interfacial tension between the phases, the partition coefficient of the active ingredient between the phases, and the product rheology. These factors combine to determine the release characteristics of the drug as well as other characteristics such as viscosity. Although a majority of semi-solid preparations contain medicinal agents for therapeutic effect, some non medicated semi-solid preparations are used for their physical effects as protectants and lubricants. In broad terms, semi-solid preparations may be classified as ointments, creams, pastes, and gels.

Ointments and creams. Ointments utilize certain bases that act as vehicles to deliver the drug and to impart emollient and lubricant properties to the preparation. Usually, but not always, they contain medicinal substances. Properties of ointments may vary from product to product depending on their specific use, ease, and extent of application. In general, ointment bases may be classified into four general groups: hydrocarbon, absorption, water-removable, and water-soluble bases.

Hydrocarbon Bases. Also known as oleaginous bases, the hydrocarbon bases are essentially water-free, incorporating aqueous preparations only in small amounts and with considerable difficulty. The primary features of this type of base include its emollient effect, retention on the skin for prolonged periods, prevention of the escape 0 of moisture from the skin to the atmosphere, and difficulty in washing off. They act

as occlusive dressings, thus increasing skin hydration by reducing the rate of loss of surface water. Also, they do not dry out or change noticeably on ageing. Hydrocarbon based semi-solids comprise fluid hydrocarbons to C30 straight-chain and branched, entrapped in a finely crystalline matrix of yet higher-molecular-weight solid hydrocarbons. The high-molecular-weight fraction precipitates out substantially above room temperature, forming interlocking crystallites. The extent and specific nature of this structure determine the stiffness of the ointment. In general, hydrocarbon-based ointments liquefy on heating because the crystallites melt. Moreover, when cooled very slowly, they assume fluidity much greater than when rapidly cooled because slow cooling leads to fewer and larger crystallites and, therefore, less total structure. Common examples of these bases include:

1. Petrolatum
2. White petrolatum
3. Yellow ointment
4. Mineral oil.

The blending of increasing quantities of mineral oil with, petrolatum can produce ointments of various consistencies as desired. For example, blending 10% w/w mineral oil with 90% w/w white petrolatum base can produce an ointment with less drag or resistance to spreading, making it ideal for application to bums or other painful areas. As illustrated in Example 2, melting the petrolatum and mineral oil together and allowing them to cool forms a soft base or vehicle. By increasing the quantity of the mineral oil in the mixture, a base is obtained that has a gel-like consistency, indicating a more viscous preparation. Hydrocarbon vehicles have several advantages, such as stability and softening; however, they, suffer from one major disadvantage – greasiness—which may stain clothing and is usually difficult to remove.

Absorption Bases. Absorption bases, as such, are hydrophilic, anhydrous materials (w/o emulsions) or hydrous bases (w/o emulsions that can absorb additional water). The addition of lanolin, lanolin isolates, cholesterol, lanosterol, or acetylated sterol renders the hydrocarbon bases hydrophilic. A typical example of an anhydrous absorption base is hydrophilic petrolatum. Here, cholesterol confers the w/o emulsion property, whereas the inclusion of stearyl alcohol and white wax enhances firmness and heat stability. Diverse additives

including cholesterol, lanolin (which contains cholesterol, cholesterol esters, and other emulsifiers), semisynthetic lanolin derivatives, and assorted ionic and non-ionic surfactants are used to emulsify water into these systems, singularly or in combination. Lanolin is probably the best-known substance for the emulsification of water in an anhydrous base. Anhydrous lanolin, USP is capable of absorbing up to 30% of its weight of water to form an emulsion. Its water-absorbing capacity is improved to 50% by the addition of cholesterol. Among the absorption bases, lanolin is the oldest and best known. However, because of its tackiness and viscous nature and reports of allergic reactions, the use of lanolin is very limited. Advents in technology have successfully produced several emulsifiers for w/o emulsions. Used in specific formulations, emulsifiers such as polyglyceryl esters form w/o emulsions. Absorption bases impart excellent emollient and a degree of exclusiveness on application.

A new group of w/o emulsifiers based on the linkage of polymethoxysiloxane chains with alkyl side chains and. polyol groups have been constituted. These emulsifiers, known as organosilicone polymers, have the capability of producing w/o emulsions with a high water content. Although the polymethylsiloxane chains possess both hydrophilic and lipophilic properties, the alkyl side chains supply the necessary lipophilic and polyol groups to provide the hydrophilic characteristics of the emulsifier. Other examples of w/o emulsifiers include cetyl dimethicone copolymer, polyethylene glycol-20-com glycerides, and a series of caprylic-capryl stearates.

Water-Removable Bases (Water-Washable Creams). These are the most commonly used o/w emulsion bases are capable of being washed from skin or clothing water. They may contain water-soluble and -insoluble components. From a therapeutic viewpoint, they have the ability to absorb serous discharges in dermatologic conditions. The water-removable bases form a semipermeable film on the site of application after the evaporation of water. As such, the base consists of three component parts: the oil phase, the emulsifier, and the aqueous phase. The oil phase, also called the internal phase, is typically made up of the petrolatum and/or liquid petrotetum. Other ingredients such as cetyl and stearyl alcohol may be added to make up the oil phase. A typical water-removable emulsion base is' hydrophilic ointment, USP. In

this base, the stearyl alcohol serves as an adjuvant emulsifier. Petrolatum in the oil phase contributes to the water-holding ability of the overall formulation. The aqueous phase contains preservative materials, emulsifier, and humectant. Humectants are added to minimize water loss in the finished composition and to add to the overall physical product acceptability. Common examples of humectants used include glycerin, propylene glycol, and a polyethylene glycol. The aqueous phase also contains the water-soluble components of the emulsion system, together with any additional stabilizers, antioxidants, buffers, etc., that may be necessary for stability, pH control, and other considerations associated with aqueous systems. Another example of an o/w emulsion base is illustrated in vanishing cream. The vanishing creams are so called because on application and rubbing into the skin, there is little or no visible evidence, of their presence. The addition of an emulsifying agent is critical to formulating an emulsion. Emulsifiers must meet the folio, wing criteria before incorporation:

1. be a surfactant to reduce surface tension;
2. be able to prevent coalescence by being absorbed quickly around die dispersed droplets;
3. facilitate mutual repulsion between particles by imparting an adequate electrical potential to the droplets;
4. be able to increase viscosity to ensure a semi-solid system;
5. be effective at low concentrations. Emulsifiers used in cream formulations may be classified into three different categories: anionic, cationic, and nonionic emulsifiers.

Anionic emulsifiers. The active portion of this class of emulsifiers is the anion. In general, these emulsifiers are more acid-stable and permit adjustment of the emulsion pH level to the desirable range of 4.5 and 6.5. Common examples include sodium lauryl sulfate and soaps such as triethanolamine stearate. Triethanolamine stearate is one of the most popular emulsifiers for creams and lotions in use today. It is usually prepared in situ during manufacture from stearic acid in the hot oil phase and from triethanolamine in the hot aqueous phase. The amount of triethanolamine controls the pH level of the resulting product.

Cationic emulsifiers. Cationic compounds are highly surface-active, but are used less frequently as emulsifiers. The cation portion of the

molecule is usually a quaternary ammonium salt including a fatty acid derivative such as dilauryldimethylammonium chloride. These emulsifiers are irritating to the skin and eyes and have a considerable range of incompatibilities, including anionic materials.

Nonionic emulsifiers. This class of emulsifiers shows excellent pH and electrolyte compatibility in emulsions, owing to the fact that they do not ionize in solution. Although non-ionic emulsifiers range from lipophilic to hydrophilic members, a typical emulsifier system may include a mixture of both a lipophilic and a hydrophilic member to produce a hydrophilic-lipophilic balance (HLB). As devised by Griffin, an HLB scale can be used to establish a range of optimum efficiency for a suitable emulsifier for a certain activity such as wetting agent, anti-foaming agent, detergent, etc. Although the numbers have been assigned up to 40, the usual range is between 1 and 20. Materials that are highly polar or hydrophilic are assigned higher numbers than materials that are less polar and more lipophilic. Generally, those emulsifiers with an assigned value between 3 and 6 are greatly lipophilic and produce w/o emulsions, whereas those in the range between 8 and 18 are hydrophilic and produce o/w emulsions. By using this scale, it is possible to relate various' emulsifiers to suitable applications. Table 3 illustrates the relationship between HLB numbers and the type of activity expected from emulsifiers. Emulsions containing non-ionic emulsifiers are prepared by dissolving or dispersing the lipophilic component in the oil phase and the hydrophilic component in the aqueous phase. The two phases are heated separately and combined. Emulsions containing non-ionic emulsifiers are generally low in irritation potential, stable, and have excellent compatibility characteristics.

Microemulsions. Microemulsions are fluid, transparent, thermodynamically stable oil and water systems, stabilized by a surfactant usually in conjunction with a co-surfactant that may be a short-chain alcohol, amine, or other weakly amphiphilic molecule. An interesting characteristic of microemulsions is that the diameter of the droplets is in the range of 100-1000 A, whereas the diameter of droplets, in a kinetically stable macroemulsion is 5000 A. The small droplet size allows the microemulsion to act as carriers for drugs that are poorly soluble in water. The suggested method of preparation of

microemulsions is as follows; the surfactant, oil, and water art mixed to form a milky emulsion and titrated with a fourth component, the co-surfactant, until the mixture becomes clear. If more oil is added to a w/o system, the system becomes cloudy, but the addition of more co-surfactant again gives a clean, transparent emulsion. Microemulsions are optically clear because the diameter of the particles in the colloidal system is less than one-quarter of the wavelength of incident light. Because of this effect, the particles do not scatter light and result in a transparent system. Microemulsions, once made, must be packaged while hot and in the liquid form. After they are cooled, they cannot be reheated and melted- because they will lose transparency because of coalescence of the oil globules to a size where they reflect light.

Water-Soluble Bases. These bases contain only water-soluble components. Water-soluble bases are also referred to as greaseless because of a lack of oleaginous materials. Incorporation of aqueous solutions is difficult because they soften greatly with the addition of water. They are better used for nonaqueoiis or solid substances. Polyethylene glycols (PEG) make up the majority of components of the water-soluble base. PEGs may exist as liquids or waxy solids, identified by numbers that are an approximate indication of their molecular weight. The lowest number signifies a liquid state, which transitions to a waxy solid state as the numbers increase. For example, PEG'400 is a liquid, whereas PEG 4000 is a waxy solid. Polyethylene glycol is a polymer of ethylene oxide and water, represented by the formula $OHCH_2$ (CH_2OCH_2) CH_2OH. They are nonvolatile, water-soluble, or water-miscible compounds and chemically inert. PEGs of interest as vehicles include the 1500, 1600, 4000, and 6000 products, ranging from soft, waxy solids to hard waxes. PEG, particularly 1500, can be used as a vehicle by itself, but better results are often obtained using blends of high- and low-molecular-weight glycols as in polyethylene glycol ointment, NF (Example 11). PEGs also serve as excellent - bases for suppository insert dosage forms. Various combinations of PEGs may be used to achieve a suppository base of desired consistency and characteristics. For example, PEG 1000 blended with PEG 4000 results in a higher melting product, whereas blending with a liquid polyethylene glycol lowers the melting point. Some drugs lower the melting points of

PEG and, therefore, each ingredient must be considered in selecting a base. The advantage of PEG suppositories is that they may be, designed to prevent melting at body temperature but rather to dissolve slowly in the body fluids. Thus, they can be prepared at temperatures higher than that of the body. They also can be stored without the need for refrigeration and do not tend to leak from the orifice on insertion because of higher melting temperatures.

Pastes. Pastes maybe defined as ointments incorporating a high percentage of insoluble particulate solids, sometimes as much as or more than 50%. The use of this high amount of insoluble particulate matter renders a stiffness to the system as a result of direct interactions between the dispersed particulates and by -absorption of the liquid hydrocarbons from the vehicles onto the surface of the particles. Because of the stiffness, they remain in place after application and are used effectively to absorb serous secretions. Pastes as such are not suited for application to hairy' parts of the body. Examples of insoluble ingredients serving as the dispersed phase include starch, zinc oxide, and calcium carbonate. Pastes make good protective barriers for the following reasons. In addition to forming an unbroken film, pastes'also absorb and neutralize certain harmful chemicals before they reach the skin surface. This last feature is attributed to the presence of insoluble particulate matter within the paste formulations. For example, for the treatment of diaper rash, when spread over the baby's bottom, the pastes absorb irritants formed by bacterial action on urine. Pastes also provide a protective layer over skin lesions and, when covered with suitable dressings, prevent excoriation of the patient's skin by scratching. Pastes afford emollient action, as do ointments. In addition, the water-impermeable film formed on application is opaque arid thus can often serve as a sunblock. Pastes are less greasy than ointments because of the absorption of the fluid hydrocarbon fraction to the insoluble particles. A clinically distinctive feature, which is generally attributed to pastes, is the ability to absorb exudates by nature of the powder or other absorptive components. Among the few pastes in use today is zinc oxide paste (Lassar's Plain Zinc Paste), which is prepared by levigating and then mixing 25% each of zinc oxide and starch with white petrolatum. The product is very firm and is better able to protect the skin and absorb secretions than is zinc

oxide ointment.

Gels. Gels are defined as semi-solid preparations consisting of dispersions of small or large molecules in an aqueous liquid vehicle rendered jelly-like through the addition of a gelling agent. Gels are an intermediate state of matter, containing both solid and liquid components. The solid component comprises a three-dimensional network of interconnected molecules or aggregates that immobilizes the liquid in the continuous phase. Gels may be classified into two primary types: hydrogels, which have an aqueous continuous phase, and organo-gels, which have an organic solvent as the liquid continuous medium. Gels may also be classified based on the nature of the bonds involved in the three-dimensional solid network: chemical gels form when strong covalent bonds hold the network together, and physical gels form when hydrogen bonds and electrostatic and van der Waals interactions maintain the gel network.

Gel-forming substances and their pharmaceutical uses. Gel-forming hydrophilic polymers arc typically used to prepare lipid-free semi-solid dosage forms, including dental, dermatological, nasal, ophthalmic, rectal, and vaginal gels and jellies. Gel vehicles containing therapeutic agents are especially useful for application to mucous membranes and ulcerated or burned tissues because their high water content reduces irritancy. Furthermore, these hydrophilic gels are easily removed by gentle rinsing or natural flushing with body fluids, reducing the propensity for mechanical abrasion. The superior optical clarity of synthetic polymer gels, such as those composed of poloxamer and carbomer has led to the current interest in developing therapeutic ophthalmic gels. Unconventional routes of drug administration by using gels and jellies are also 'being explored. Thus, two nasal jellies were developed and marketed. The intranasal vitamin B-12 gel, Nascobal (Schwarz Pharma), is used as a dietary supplement. The gel base is composed of a hydrophilic cellulose derivative, the exact nature of which is not disclosed. However, the gel is apparently odorless and nonirritating, and adheres well to the mucous membrane. Neo-Synephrine Viscous (Sanofi Winthrop) is a water-soluble nasal jelly formulated with melhylcel-lulose; it contains the decongestant phenylephrine hydrochloride.

In addition to serving as drug-containing vehicles, some gels have other important functions. For example, a soft, flexible gel applied to burned skin can prevent excessive water loss by forming a physical barrier. Ocular gel inserts are designed to lubricate the eye continuously and promote healing. Still other gels are intended for lubricating surgical and medical instruments in order to minimize local irritation.

Many gel-forming substances are available for preparing pharmaceutical gels- and jellies. Although these substances share some common physical characteristics, the intended use may require gelling attributes of a certain substance or blend of substances.

Proteins. **Collagen** is the major connective tissue protein in animals. The collagen molecule is considered to be a block copolymer, formed with blocks of glycine (33%) and proline and hydroxyproline (23%), between blocks of the remaining amino acids (44%). Tropocollagen is the asymmetrical subunit of collagen, which is made up of three peptide chains wound in a triple helix. The nonhelical portions of collagen, so-called telopeptides, are susceptible to enzyme digestion. Native collagen is insoluble • in water, but 2% to 3% may be solubilized in dilute acidic solutions. Collagen-may also be solubilized by treatment with proteolytic enzymes, which digest the telopeptide portions (e.g., yifrogen, Collagen Corp.). The asymmetrical molecular structure of collagen permits the formation of rigid gels; highly rigid structures are obtained at 0.1% concentration by UV irradiation or chemical crosslinking with aldehydes. These gels are used as biomaterials for-vitreous replacements. Pepsin- solubilized collagen forms clear, rigid gels; they are prepared with a 0.2% to 6.4% collagen solution, which consists of unassociated molecules and small fibrils when cooled to ~5 °C. As the temperature is raised to 37 °C, the collagen molecules aggregate, forming subfibrils that further aggregate to form the gel network. The rigidity is then increased by lightly crosslinking with aldehydes.

Optically clear collagen gels have been considered for use in ophthalmic drug delivery. Ocular inserts of succinylated or methylated collagen are patented as soluble devices for drug delivery. Constant, controlled release of pilocarpine hydrochloride was maintained for 5 to 15 days with crosslinked collagen and other collagen-derivative inserts.

A corneal shield made of non-crosslinked collagen is marketed as Bio-Cor by Bausch & Lomb. This shield is placed over an eye injury and, as collagen slowly dissolves, the cornea is continuously lubricated to promote healing. Collagen implants (Lacri-medics) are also used for relief of dry eye by partially blocking tear removing canals; the implants dissolve within 7 to 10 days. Collagen gels are also used in hemostasis. A lightly crosslinked sterile pad, Instat hemostat (Johnson &Johnson), assists in forming blood clots to arrest bleeding during surgery.

Gelatin forms elastic gels reversibly by cooling solutions that contain a sufficient concentration. The gel microstructure consists of a three-dimensional network' held together by junction zones in which gelatin chains have partly refolded into the triple helix of the parent collagen molecule. The physical properties associated with gelatin gels depend on protein concentration, average molecular weight, temperature, pH, and additives.

The swelling kinetics of uncrosslinked type B gelatin films in the absence and presence of additives was studied. The water-swelling kinetics of chemically crosslinked matrices were considered for controlling the release of therapeutic agents. Heat-crosslinked gelatin matrices were also examined for drug release. Both, the molecular weight between crosslinks, M,- and the mesh size between crosslinks, J, were used to characterize gelatin gel matrices during release of the macromolecular solute dextran. The crosslinking extent and density in gelatin matrices was directly determined by chemical analysis of the uncrosslinked primary amino groups and compared with swelling parameters of crosslinking.

Although gelatin has been used by the pharmaceutical industry for mainly producing soft and hard gelatin capsules, some commercial products use a hydrated gel form. The sterile product, H.P. Acthar Gel-(Rorer), contains 16% gelatin for sustaining the release of adrenocorticotropic hormone from an intramuscular or subcutaneous injection. A sterile, absorbable gelatin sponge, Gelfoam (TJpJohn), which has a lightly crosslinked matrix, is used during surgery to absorb blood and promote clotting. An absorbable gelatin film, Gelfilm Ophthalmic (Upjohn), is available for use in ocular surgery. The ocular implant requires 2 to 5 months for complete absorption.

Polysaccharides. **Alginates.** Alginic acid is processed from brown seaweed, using a dilute acid, followed by alkalinization with soda ash to yield the water-soluble salt form, sodium alginate. Alginic acid is a linear glycuronoalycan composed of polyman-nuronic acid blocks (M), polygluuronic acid blocks (G), and mixed blocks of these two uronic acids (MG). The gelling properties and gel microstructure of the various salt forms of alginic acid depend on the M, G, and MG block content. High- M alginates form turbid, weak gels, and high-G alginates form transparent, brittle gels. Gelation depends on the cation type; sodium alginate gels are water-soluble, whereas calcium alginate gels are insoluble, yet swell in water. Many "egg box" junction zones are formed by calcium cations and G blocks to create such rigid gel networks.

Sodium and calcium alginate are used in commercial pharmaceutical formulations. Sodium alginate gels have superior spreading and. lubricating properties; they are also nontacky and tasteless, and have emollient qualities. Moreover, sodium alginate is compatible with many compounds such as starch, sodium carboxymethylcellu-lose, pectin, carrageenan, 25% ethanol, 4% sodium chloride, and most alkali salts. Taking advantage of this compatibility and the favorable gel properties, sodium alginate is formulated with sodium carboxymethyl cellulose in the nonirritating, water-soluble lubricating jelly, Ortho Personal Lubricant (Ortho). Calcium alginate is used as a wound dressing for -varicose, and decubitus ulcers, where it forms a hydrophilic gel over the wound by. absorbing exudate, which promotes healing. The high rigidities of calcium alginate gels make them suitable for preparing dental impressions and as matrix barriers for controlling drug delivery. Theophylline release was studied from granules coated with sodium alginate and calcium lactate through insoluble gel formation.

Carrageenan, a sulphated polysaccharide extracted from red seaweed, may be separated into' a number of fractions depending on the species, Season,' and environment. The three major fractions, lambda-, iota-, and kappa (K)-carrageenan, contain an alternating sequence of (1 -r 4)-linked (3-D-galactopyranosyl and (1 – 3)- linked a-o-galactopyranosyl residues, but they differ in the degree and sites of sulfation. Of these three fractions, only lambda-carrageenan cannot form gels.

Under optimal ionic strength and polymer concentration, K-carrageenan forms rigid, thermoreversible gels in the presence of cations. The elastic moduli of these gels depend on the type of cation and follow the Iloftneister series: $Cs^+ > Rb^+ > K^+ > S > Na^+ > Li^+$. The K-carrageenan gel also undergoes syneresis, the spontaneous liberation of liquid from the matrix. Early models for gelation envisioned multihelical junctron zohes composed of polysaccharide chains folded into double helices. This model was extended to accommodate cations, in that the formation of the helical domains would require mediation by the cations themselves. However, other- researchers propose an indirect role for cations in which they alter solvent structure around the K-carrageenan helices, thereby inducing gel formation. Differential scanning calorimetry and isothermal titration calorimetry were used to study mono- and divalent cation binding and induced conformation changes in K-carrageenan.

Gels made with K-carrageenan and potassium ions have excellent lubricity and emollient properties. Because of such favourable gelling characteristics, these gels are used as vehicles for the topical administration of drugs and as gelling agents in other pharmaceutical, preparations. They can also be used in combination with sodium carboxy-methylcellulose, which interferes with gel formation, resulting in a variety of consistencies and textures. Theophylline and diclofenac sodium release were studied from tablet matrices containing K-carrageenan and iota-carrageenan with KC1 or $CaCl_2$.

Hyaluronic acid is a linear glycosaminoglycan (an aminopolysaccharide), which is an important component of synovial fluid and the cellular matrix of connective tissue. It comprises a biological gel that supports cells, maintains tissue hydration, and functions as a lubricant and shock absorbent in joints. Hyaluronic acid forms transparent, rigid gels at 2% concentration, although (hey are not as rigid as agar and carrageenan gels. The gel microstructure is constructed by entanglement couplings among the long polysaccharide chains, which have molecular weights ranging from about 1×10^6 to 4×10^6 Da, depending on the source of animal tissue.

A 1% viscoelastic jelly of the sodium salt is commercially available as Healon (Kabi Pharmacia), which is widely employed in ophthalmic

surgery. Sodium hyaluronate jelly provides a non-irritating viscoelastic medium for separating tissues during surgery and prevents postoperative adhesion formation. Investigators in a clinical trial of intra-articular injections of 500-730 kDa sodium hyaluronate (Hyalgan, Sanofi) for osteoarthritis concluded that this treatment might slow downthe structural progression of the disease. When hyaluronic acid was tested as an ophthalmic gel, its mucoadhesive properties improved the ocular bioavailability of tropicamide.

Pectins are a complex group of polysaccharides, the structures of which vary' with plant source. They are heteropolysaccharides that are extracted from, apple pomace and citrus, fruit rinds and consist mainly of polygalapturonic acids. The degree of esterification determines the gelling process and, hence, the eventual commercial use. High-methoxy (HM) pectin gels in the presence of high concentrations of sucrose at acidic pH. The sucrose dehydrates pectin to a gel. High- methoxy pectins are used in sweet food products such'as fruit jams and preserves. In contrast, low-methoxy (LM) pectins gel -in the presence of divalent cations, especially calcium, by the “egg box” mechanism proposed for alginates. Moreover, calcium pectinate gels prepared at neutral pH are heat stable, whereas acidic pH gels are thermoreversible. Gel strength depends on the extent of esterification (levels from 30% to 50% are optimal), the distribution of ester groups on the chain, and the average molecular weight. LM pectins have been used traditionally in antidiarrheal formulations with kaolin. HM pectins were evaluated in controlled release matrix formulations. Pectin micro-spheres were reported to improve ophthalmic bioavailability of piroxicam in rabbits compared with commercial piroxicam eye drops.

Starch is the principal polysaccharide of higher plants and can be extracted from a number of sources, including corn, wheat, and potato. Starch granules can be fractionated into two structurally distinct polysaccharides: 30% amylose (linear polymer) and 80% amylopectin (branched polymer). Starch is insoluble in cold water because of extensive hydrogen bonding between polysaccharide chains. However, the hydrogen bonds break at temperatures above the gelatinization range of 60 °C to 70 °C, allowing the granules to swell. The starch sol can then form a gel on cooling. The type of gel depends on the starch species; corn

starch forms opaque, rigid, gels, whereas potato starch forms clear, non-rigid gels.

The microstructure of starch gels is an example of a matrix strengthened by filler. Heating causes the amylopectin—granules to become swollen and porous, whereas the linear araylose phains dissolve. As the solution cools, amylose sets-into a gel matrix diet threads through the porous amylopectin granules, thereby producing a reinforced gel. Aqueous starch solutions exhibit retrogradation, in which crystalline aggregates form spontaneously over time with Browniaii movement. As the solution ages, it becomes opalescent, followed by the gradual precipitation of starch. Starch gels are also unstable because of the formation of crystalline aggregates; however, they undergo synaeresis. The amylose fraction is responsible for these instabilities; amylose chains are linear, enabling them to become parallel in order to form aggregates. Starch has been used extensively as a pharmaceutical excipient in tablets, serving as a filler, binder, and disintegrant. Starch gels have found limited use as skin emollients. Starch has been examined as a mucoadhesive in microparticles to improve protein uptake across the nasal mucosa.

Semisynthetic Polymers (Cellulose Derivatives). **Carboxymethylcellulose, sodium** (NaCMC) is a carboxy-methyl ether of cellulose, the ubiquitous polysaccharide composing the fibrous tissue of plants. The hydroxyl groups on the 2- glucopyranose residues of cellulose are replaced by carboxymethyl groups; the number of replacements is known as the degree of substitution DS. Both the DS and polymer chain length determine the solubility, viscosity, and gel strength of NaCMC. It dissolves in water and mixtures of water with the lower alcohols and glycerin. Aqueous gels are stable from pH 2 to 10 but susceptible to microbial growth.

The microstructure of NaCMC gels was examined on freeze-fractured samples with a transmission electron microscope. A fine, quasi-crystalline structure consisting of filaments with thicknesses of 2 to 3 nm was identified. These filaments are microaggregates of individual polymer chains. The rigidity of NaCMC-gels can be increased by adding multivalent cations such as Al^{3+} or Fe^{2+}, resulting in ionic bridges between the cations and ionized carboxyl groups. These gels are

stable indefinitely.

Hydroxypropyl methylcellulose (HPMC) is produced similarly to hydroxypropyl cellulose, except that methyl chloride is included in the reaction. The composition of the substituted hydroxyl groups ranges from 3% to 12% hydroxypropyl and from 19% to 30% methyl. HPMC is soluble in cold water and the polyethylene glycols up to 600 Da, but, in contrast to hydroxypropyl cellulose, HPMC is not soluble in alcohol. It is also less susceptible to hydrolysis, and is stable from pH 3 to 11. Aqueous gels are formed on heating; the gel point ranges from 50 °C to 90 °C, depending on the grade. Addition of small amounts of water-miscible solvent, such as ethanol and the glycols, raises the gel point. The good lubricating and adherent qualities of HPMC gels are exploited in Xylocaine 2% Jelly (Astra), which is used to minimize discomfort associated with medical procedures. A 2% solution (80 kDa) is commercially available as an ophthalmic surgical aid (OcuCoat; Storz). The influence of indomethacin, propranolol HC1, and tetracycline HC1 was studied on the properties and swelling characteristics of matrix gels containing hydroxypropyl methylcellulose and methylcellulose.

Methylcellulose is a cellulose ether in which methyl groups have been substituted for hydroxyl groups on the 2-glucopyranose residues. It is soluble in cold water at low methoxy contents; increased substitution increases the solubility in hydroalcoholic and alcoholic solutions

Aqueous solutions of methylcellulose gel on heating, whereby micelle-like junction zones form throughout the network. Gel strength and gelling temperature depend on, the concentration, degrees of substitution, and average molecular weight. The gelling temperature can be lowered by adding sugar or most electrolytes, which reduce polymer hydration.

High viscosity grades of methylcellulose are used in pharmaceutical gels. The gels are demulcent and have good surfactant properties, which permit easy spreading on body tissues. Therefore, methylcellulose gels are used as dressings for burned tissue because they minimize water loss and are easily removed. The high viscosity grades are used in ophthalmic preparations such as Murocel artificial tears (Bausch & Lomb) and Neo-Synephrine viscous solution (Sanofi WinthrorX). Other

pharmaceutical applications include the bulk-forming laxative, Citrucel (SK-Beecham), and lubricating jellies for surgical and medical procedures. A methylcellulose gel was investigated for topical administration of tetracycline HC1. The bioadhesive properties of 3% methylcellulose gels on slowing mucociliary clearance were examined using a rate model.

Synthetic Polymers. **Carbomer** is a synthetic polyacrylic acid resin, which is copoiymerized with about 0.75 to 2% polyalkyl sucrose. This is the reason why aqueous dispersions of carbomer must be protected against microbial growth: Carbomer is a high molecular weight polymer that contains carboxylic acid groups on about two thirds of its repeat units. Gels are formed on neutralisation between pH 5 and 10 with methal hydroxides or amines, such as diisopopanolamin and triethanolamine.

The molecular size of carbomer is important in determination of gel properties and application. Carbomer 934 and 940 with average molexular weights of 3^{-106} and 4^{-106}. Da, respectively, are most commonly used by the pharmaceutical industry. The gels can be formed with large quantaties of alcohol, but the alcohol dehydrates the polymer network and lowers the viscosity.

Poloxamer Poloxamer is the generic name for a series of block copolymers that are composed of one polypropylen oxide block sandwiched between polyethilen oxide block.

At relatively high concentrations (>20%), poloxamers form thermoreversible gels; however, they gel on heating rather than cooling. Thr amphiphilic nature support the gelling mechanism of poloxamers, where micelle-like junction zones, form at or above room temperature. The junction zones consist of large populations of micelle-like structures, which apparently form a viscous, liquid crystalline phase. Poloxamers can also form gels in dilute hydroalcoholic solutions.

Poloxamer gels have many characteristics favourable for use as artificial skin, which is helpful in treating third-degree bums. The gels are non-toxic, enhance healing by controlling water, heat, and electrolyte loss, and provide detergent activity on wound debris. Because of poloxamer's inverted thermoreversibility, cool solutions can be poured onto damaged tissue, forming gels when warmed to body, temperature.

The gels are easily removed by rinsing with cool water.

Poloxamer gels mimic mucus and are optically clear, which makes them suitable for ophthalmic drug delivery. A poloxamer gel formulation containing pilocarpine showed improved bioavailability over an aqueous solution of the drug. Release kinetics of lidocaine, diclofenac, and hydrocortisone from topical poloxamer gels were also assessed. Subcutaneous injection of insulin loaded poloxamer' gels prolonged the hypoglycemic effect of insulin in rats. Commercial topical gels include AquaTar (Allergan Herbert), a poloxamer-407 base that contains coal tar, and Benzac W (Galderma), a blend of poioxamer-182 and carbomer-940 gels, that contains benzoyl peroxide.

Polyacrylamide (PAAm) is a hydrophilic polymer that absorbs and retains large volumes of water. However, aqueous solutions of PAAm, especially the high molecular weight species, undergo physical ageing, which results in a decrease in viscosity. PAAm is soluble in hydrophilic nonaqueous liquids such as glycerol, but insoluble in methanol and ethanol.

Polyacrylamide forms water-based gels at concentrations around 4% w/v, which exhibit pseudoplastic behavior. A PAAm ophthalmic gel containing pilocarpine was compared with other gel vehicles; the ocular bioavailability of the PAAm gel was three times greater than that of the aqueous control solution. The.kinetics of ibuprofen release for cross-linked PAAm gels was studied. A kinetic model was proposed for swelling induced loading of insulin into cross-linked PAAm gels.

Polyvinyl alcohol (PVA) is a hydrophilic, synthetic polymer that is prepared indirectly by hydrolysing polyvinyl acetate. It cannot be produced by direct polymerization of vinyl alcohol because the monomer is unstable. The chemical structure of PVA is simple, consisting of a carbon-chain backbone with alternating hydroxyl groups; it favours the formation of crystalline aggregates in solutions, gels, and solids. PVA is soluble in water, glycerin, and mixtures of water with the lower alcohols; however, it can be precipitated from aqueous solutions with sulfates and phosphates. The gelation of PVA occurs in more concentrated solutions; the gel point of 10% PVA in water is around 14 °C. In general, gel strength depends on the degree of crystallinity of a particular sample.

Polyvinyl alcohol is used in ophthalmic preparations, serving as a mucus mimicking (mucomimetic) agent in artificial-tear formulations such ds Liqdifilm Tears and Liquifilm Forte (Allergan). Physically crosslinked PVA hydrogels, prepared by low-temperature crystallization, were tested as vehicles for the rectal administration of indomethacin. Chemically cross-linked PVA hydrogels have been considered for soft contact lenses. Both, the molecular weight between cross-links, Me, and the mesh size between cross-links, J, were used to characterize a covalently cross-linked polyvinyl alcohol gel during evaluation of bovine serum albumin (BSA) release. PVA hydrogel nanoparticles loaded with albumin into poly-lactic/glycolic- acid microspheres released albumin up to two months. The release of water-soluble pseudo-ephedrine was studied from compressed swellable-soluble PVA matrices.

Inorganic Substances. **Aluminum hydroxide** forms a two-phase gel consisting of a network of discrete solid particles in water. Aluminum hydroxide gels are soluble in acidic and extremely basic media, and are compatible with many additives, including glycerin, saccharin, and some preservatives.

The aluminum hydroxide gel exhibits thixotropic behavior, in addition, gel stability is enhanced by polyols such as mannitol and sorbitol. However, unlike other gels, aluminum hydroxide gels do not have demulcent properties; they are used mainly as an oral antacid preparation.

Smectite clays. Bentonite and hectorite clays, consist primarily of hydrated aluminum and magnesium silicates, respectively. Bentonite is recognized for its swelling capacity; one gram can absorb up to 11 ml of water. A commonly used smectite clay is aluminum magnesium silicate (Veegum, R.T. Vanderbilt Co.). These clays have plate-like particles, 1 to 2 /zm in size, that form well-ordered gel mesophases spontaneously on contact with water. The gels are formed at about 5% concentration, and are presumably stabilized by opposite electrostatic charges between particle edges and faces. Therefore, these smectite gels are incompatible with strong electrolytes, and in particular with di- and trivalent cations. The gels also exhibit plastic flow; they have static yield values and are tbixotrppic.

Laponite clay also belongs to the smectite class, but is a synthetic, gelling agent. Like bentonite, laponite swells considerably in water—but only a 2% concentration is needed to form a gel. Laponite does not contain impurities, which is an advantage over the natural clays; however, some electrolyte must be included in the water to support the gijl microstructure.

Smectite clays are used by the pharmaceutical industry as mainly suspending and thickening agents. Because of the net negative charge of these clays, cationic drugs can be adsorbed by an ion-exchange mechanism. Release of metronidazole from bentonite complexes was inhibited at acidic pH, but increased significantly at pH 7. Simple gels containing hectorite and gelatin were investigated for rectally administrating insulin to rabbits. Finally, the iontophoresis transdermal transport of calcium from a paste of calcium-enriched bentonite was studied using, excised pig skin.

Parabens

The two most widely used agents are methylparaben and propylparaben. They are effective against molds and yeasts, but less effective against bacteria. They are more effective against Gram-positive than against Gram-negative bacteria. Parabens are most active at acidic pH levels, less so in alkaline media. They are usually-combined; an effective combination is 0.20% methylparaben and 0.05% propylparaben.

Dowcill 200 (Dow Chemical'Co., Midland, MI) is a water-soluble, broad spectrum antimicrobial and antifungal compound. It is not inactivated by non-ionic, cationic, or anionic formulations, and it is particularly effective against Pseudomonas. Its activity is independent of pH; effective concentration is 0.02-0.30%.

Glydant (MDMH) (Lonza, Inc. Fairlawn, NJ): dimethylol-5,5,dimethylhydantoin is a water-soluble, highly active, broad-spectrum preservative. It functions over a wide range of temperatures and pH levels. It is 'non-corrosive, lexicologically acceptable, and biodegradable; effective concentration is 0.005-0.10%.

Germall 115 (Sutton Laboratories, Chatham, NJ): imidazolidinyl urea is a hygroscopic water-soluble white powder compatible with essentially all. cosmetic ingredients including surfactants, proteins, 'and other

special ingredients. Germall 115 acts synergistically with all other preservatives. It is effective against Gramnegative bacteria, including Pseudomonas. Combined with para-bens, it provides a broad spectrum of activity against yeasts and molds. It is recommended in the combination of Germall 115, 0.30%; methylparaben, 0.20%; and propylparaben, 0.01%.

Germall II (Sutton Laboratories, Chatham, NJ): diazolidinyl urea is a watersoluble, hygroscopic powder effective, against Gram-positive and Gram-negative species including Pseudomonas. It is synergistic, with other preservatives, including the par-abens. It is 'not inactivated by surfactants, proteins, or emulsifiers and is effective at all usual pH levels. It's recommended in the combination of Germall II, 0.20%; methylparaben, 0.20%; and propylparaben, 0.10%.

Germaben II-E (Sutton Laboratories, Chatham, NJ) is a clear liquid preservative system, readily soluble at concentration of 1.0% in both w/o and o/w emulsions, but in water alone. It has the composition of Germall II, 20%; methylparaben, 10%; propylparaben, 10%; and propylene glycol, 60%.

Suttocide A (Sutton Laboratories, Chatham, NJ) is a 50% aqueous solution of sodium hydroxymethylglycinate. It is a broad-spectrum antimicrobial preservative active against Gram-positive and Gram-negative bacteria and against yeast and mould. It remains active at alkaline pH levels.

LiquaPar Oil (Sutton Laboratories, Chatham, NJ) is a 100% clear, active, stable liquid blend of isopropyl, isobutyl, and n-Butyl esters of /7-Hydroxybenzoic acid. This combination of parabens is a very effective preservative even at low concentrations against Gram-positive and Gram-negative[A] bacteria, yeasts, and moulds. The higher alkyl esters are more active and more stable and resistant to hydrolysis, than are the lower alkyl esters; effective concentration is 0.1-0.4%

Busan 1504 (CTFA) (Buckman Laboratories, Memphis, TN): dimethylhydroxy- methylpyrazole is a wafer-soluble, broad-spectrum bactericide and fungicide compatible with anionic, cationic, and non-ionic ingredients. It is stable over a broad pH range and compatible with proteins; effective concentration is not given.

Ethylenediaminetetraacetic acid (EDTA) is a chelating agent that

binds certain metals, especially iron and copper, which are essential to the nutrition of certain microorganisms. In this manner, it is a strong booster or enhancer of the activity of preservatives (27, 28) especially the • parabens. Alone, it has the ability to increase the permeability of the bacterial cell wall and can kill Pseudomonas aeruginosa and E. coli by this activity; effective concentration is 0.05-0.10%. Several factors may influence the success or failure of a preservative to protect a formulation against microbial contamination. These factors include the interaction of the preservative with surfactants, active substances, other components of the vehicle, sorption by the polymeric packaging materials, and storage temperature. Although hundreds of chemicals can function as germicides, only a few substances have made it to the marketplace. The small' list is not based as much on a compound's effectiveness as an antimicrobial agent as on the compound's safety and effectiveness in the final product

The packaging of semi-solid products, usually in jars and tubes, represents the best and worst conditions for microbial contamination. When using jars, the risk of contamination is higher every time a jar is opened or each time fingers touch the product. For these reasons, semi-solid products in jars require a highly effective, long acting preservative system to remain active throughout the' life of the product. With tubes, the risk of microbial contamination is significantly reduced because they expose only a very small area each time a cap is removed. Tubes also -provide control of dose by .an amount expressed with minimum exposure to the environment or human contact. Therefore, because products packaged in tubes are less likely to become contaminated, the use of preservative is also reduced. Thus, products packaged in tubes are less likely to cause skin irritation or sensitization.

The general principles of manufacture of medicines in the form of ointments in view of rules of GMP. The big assortment and a variety of physical and chemical properties, the medicinal and auxiliary substances used in ointments, demands various technological (dissolution, disintegration, homogenization, etc.) receptions which are necessary for taking into account at the organization of their manufacture with the purpose of reception of a standard (qualitative) product. Most precisely and correctly to formulate conditions on performance of technological

receptions during all production cycle (a premise, equipment, technological process, stage-by-stage quality assurance of production) is possible only on the basis of knowledge of properties of compound components and disperse medicinal system as a whole, and also the general principles and rules of the Good manufacturing practice—GMP).

Requirements to manufacturing rooms and the equipment

With the purpose of realization of requirements GMP on a site of manufacture of ointments all rooms have the necessary areas and answer a class of cleanliness *C*, that is provided with use of special designs, materials, and also two-level system of ventilation.

The initial raw material from a room of preparation of raw material after weighing is transferred in capacities from the stainless steel, closed by covers, to a room for preparation of ointments through a special window. The initial raw material is loaded into reactors through hatches and the flexible reinforced pipelines with the help of vacuum. Loading hatches of reactors are closed by covers.

During preparation of ointments, the following equipment is used: reactor for fusion of components; reactors for grinding and mixing of substances; vacuum mixers—homogenizers; dispersers.

All equipment is united by demountable pipelines for transportation of intermediate production. For example, not packaged ointment from a vacuum mixer—homogenizers under pressure of compressed cleared air is passed in the Muller drum emptying container, intended for time storage and transportation of intermediate production. The filled container is closed hermetically and transported in a roof for packing ointment.

On a site of packing, the system of submission of ointment in the bunker of the tube-filling automatic machine is joins to "muller container".

The equipment for manufacture and packing of ointment (reactors—mixer, collections, capacities for transportation of intermediate production, and also the automatic device for its packing) is hermetically closed, that allows using vacuum and pressure at loading and an unloading of production. All this provides safety of intermediate production from microbe and cross-contamination with volatile substances, and also possible evaporation of water or absorption of

moisture during all production. The equipment from a glass is not used. All parts of the equipment which contacts to production are made of high-quality stainless steel 316L. Material pipelines in places probable "dead zones" are executed from the reinforced transparent polyethylene that enables to determine presence of the rests of production and due to flexibility of hoses to delete them. The design of all pipelines provides their fast and easy disassembly for washing and disinfection.

Requirements to manufacture of ointments

1. The control over quality of water which is used for the various purposes, its conformity to requirements of normative documents (specifications) on microbic cleanliness is provided by GMP.
2. The system of quality at the manufacturing firm should provide development of specifications on all kinds of intermediate production according to requirements of GMP. It is necessary to supervise not only the quality of an intermediate product which is transferred from an industrial site to a site of packing, but also the intermediate product received at all stages.
3. Quantitative transfer of initial raw material and intermediate production with the help of pipelines to destination is provided by GMP.

In system of pipelines there should not be "dead zones", the amount of the transported production should be supervised, and the rests should to leave. This requirement can be provided with the help of various technical decisions. For example, into the pipeline of the system of automatic submission of ointment on a site of packing it is inserted a special silicone sphere which, moving under pressure, deletes the rests of production from the pipeline.

4. Conditions of transportation, packing, and other industrial operations where pressure or temperature is used should not change rheological and other characteristics of intermediate production. For example, by manufacture of ointment on a hydrophilic basis during transportation, and it is especial at packing in tubas viscosity approximately twice decreases. At use of the rotary-pulsating device can, occur "air bubble nucleation" in the production (arise gas emulsions).
5. With the purpose of protection of intermediate production, initial raw material, primary packing and clean containers from pollution the materials intended for an industrial site of soft medical products, act

in a special airlock where are released from transport container and secondary packing. If necessary, primary packing is cleared and washed, then the initial raw material is transferred to a room of preparation of raw material where weight (volumetric) operations are carried out.

6. According to requirements of the GMP, the amount of made production should correspond to capacity and productivity of the used equipment.

7. To guarantee quality of ointments as heterogeneous disperse systems, the special attention is given maintenance of uniform distribution of all components during preparation of intermediate production and its packing in primary packing, and also a consistence of packed up production. It is not authorized to pack up production in a liquid condition, except for cases when at validation it has been established, that such conditions do not influence quality of finished goods.

Non-uniform distribution of components in intermediate production results in its non-uniform batching. In order to prevent this phenomenon the reactors—mixers intended only for preparation of soft medicines with the various types of agitator are used:

- anchor agitator with the Teflon scraper, which warns local overheating and sticking of weight to walls of a reactor;
- contra-rotating internal blades, providing effective weight hashing;
- turbine type "POLYTRON", mainly for emulsification or suspendation micronization powders.

Disperser such as MEGATRON it is applied to manufacture of ointments—suspensions when are used nonmicronisation powders.

It is joined to a reactor that allows to carry out dispersion in the liquid environment in the closed cycle. As for dispersion there is non-desirable heating suspension, the system is equipped by heat exchanger such as “a pipe in a pipe”. It enables to avoid heating of suspension (conducts to superfluous dissolution of crushed substance with the subsequent unguided process isohydric crystallization or salting-out) and decrease in quality of production.

Packing emulsive and suspension ointments in a liquid condition can lead to their non-uniform batching as a result of stratification of disperse systems, and also to disturbance of stability. Therefore, the bunker of the

tube-filling automatic machine for packing ointments is in addition supplied with an agitator.

8. At preparation of the ointments containing water or other solvents, and also substances absorbing moisture, during all technological process the conditions resulting in a minimum of evaporation of liquids or absorption of a moisture from an environment arc provided. Manufacture of ointments is carried out with use of the equipment (reactors, dispersers, containers for time storage of intermediate production) which hermetically is closed, that results in the minimal evaporation of liquids and absorption of moisture.

9. During all manufacture of ointments, including a stage of packing, the opportunity of foaming is not supposed or reduced to a minimum.

Formation of gas emulsion can lead to non-uniform batching of intermediate production, loss of stability during storage, to discrepancy of capacity of primary packing and volume of the packaged ointment.

Therefore, on development of technological process design features of the equipment (accommodation of agitator), and also properties of received production are taken into account. At presence of an opportunity of foaming or formation “air bubble nucleation” in production technological process is carried out under vacuum.

10. Time and conditions of storage of intermediate production before its packing in primary packing are determined and are strictly maintained. Long storage of intermediate production in a reactor or the collection can lead to change its physical and chemical (rheological) properties and will demand additional processing (heating, hashing, etc.). For example, at ointment with expressed thixotropic properties at storage structural viscosity appreciably grows that complicates in subsequent its unloading and packing in primary packing. Independent processing of such ointment can change its quality.

11. Sufficient tightness of primary packing with packaged production is provided.

Tubas for ointments, creams and gels should have a latex ring for its hermetic scaling at seaming. Besides, the protective membrane should not have damages and microcracks. Otherwise, infiltration of components and change of quality of a preparation are possible (due to evaporation or absorption of a moisture), loss of stability (as a result of

contact to an environment), deterioration of appearance of primary and secondary packing, is possible also microbic contamination during storage.

12. The requirement of strict sequence is maintained: packing of intermediate production in primary packing, labelling, and packings in a secondary packing material and group container.

On a site of packing the tube-filling automatic machine, an automatic packing machine and automatic system of drawing of series are united in one system—packing, packing and drawing of series.

13. On a site of soft medicines in the same rooms, various kinds of production are not made simultaneously. Disturbance of this rule can lead to deterioration of made production (contamination by volatile substances) and to discrepancy to requirements of the normative document on section “Description”.

QUESTIONS ON THE TOPIC

1. Determination of ointment, paste, cream, gel, and liniment as a dosage form.
2. Classification of soft medicinal forms (MLF).
3. Requirements for ointments.
4. Classification of the bases for the production of ointments and the requirements imposed on them.
5. The main stages of the manufacturing process MLF.
6. Characteristics of technological equipment used in the production of MLF. Types of mixers.
7. Methods of preparation and equipment used in the production of suspensions and emulsions.
8. The device and principle of operation of propeller and turbine stirrers.
9. Features of preparation of emulsion and suspension preparations.
10. Evaluation of the quality of soft medicinal forms according to NTP.
11. Packaging and storage conditions for soft medicinal forms.
12. Suppositories. Fundamentals, manufacturing technology.

TEST YOURSELF

1

The pharmaceutical company plans to release suspensions. Specify the equipment that can be used to simultaneously disperse and homogenize heterogeneous systems:

* A) Rotary pulsation apparatus
B) Mixer reactor
C) Disintegrator
D) Mixer with paddle mixers
E) Propeller mixers

2

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3

The pharmacist prepared a suppository mass with novocaine and cocoa butter, but it turned out to be fragile. Specify the substance to be added to form the plastic:

* A. Lanolin anhydrous
B. Lanolin aqueous
C. Paraffin
D. Vaseline
E. Squeal

4

Suppositories are prepared in the pharmacy by various methods. Specify the method of preparation of rectal suppositories
on cocoa butter:

* A. Deflation
B. Tablets
C. Granulation

D. Pouring
E. Extraction

5

The pharmacy received a prescription for ointment. Specify the method of administration of ointments soluble in water in the amount of more than 5%:

* A. Enter the type of suspension of the molten base
B. Purified in water
C. Dissolved in molten base
D. Dissolve in a suitable liquid base
E. Add in the end to the finished ointment

6

The patient needs to prepare rectal suppositories by casting. Specify a hydrophilic base for the following suppositories:

* A. Polyethylene oxide
B. Cocoa butter
C. Butyrol
D. Lazupo
E. Vitepsol

7

The pharmacy received a prescription for the preparation of a dermatological ointment of benzylpenicillin. Specify the type of ointment prepared:

* A. Ointment-suspension
B. Ointment solution
C. Ointment-emulsion
D. Ointment-alloy
E. Combined

8

The pharmacist prepares the extraction ointment. Specify the component that should be used for the preparation of ointments of this type:

* A. Calendula flowers
B. Calendula tincture
C. Aloe juice
D. Fingertip extract
E. Rutin

9

During the production of suppositories by the method of pumping after the introduction of cocoa chloral hydrate in the oil, suppository mass became viscous and began to flow. The substance should be added to the suppository mass to restore density and plasticity?

* A. Squeal
B. Glycerin
C. Water purified
D. Dimexide
E. Starch

10

What amount of base should be used to prepare the drug according to the spelling:

Rp.: Anaesthesini 0.1 Xeroformii 0.5 Olei Cacao 2.4
M. ut fiant suppositoria numero 10
Yes. Signa. 1 candle per day, rectally

* A. 24
B. 25
C. 30
D. 36
E. 40

11

When preparing a dermatological ointment, adding which substance will create an ointment-emulsion:

* A. Protargol
B. Streptocide
C. Menthol
D. Resorcinol
E. Bismuth Subnitrate

12

Different types of bases are used in the manufacture of soft dosage forms. What is the basis of the hydrophilic when administered below?

* A. Polyethylene oxide
B. Vaseline
C. Animal fat
D. Hydrogenated fats

E. Petrolatum

13

What substances can be used as gelling agents in the production of gels?

* A. Cellulose derivatives, carbomer
B. Starch, magnesium oxide
C. polyethylene oxide, solid fat
D. Glycerin, vegetable oils
E. Vaseline, lanolin

14

Specify the mass of rectal suppositories, unless indicated in the recipe:

* A. 3.0
B. 2,0
C. 4,0
D. 1,5
E. 5,0

15

A pharmacist preparedgelatin-glycerin based. Specify the ratio of gelatin, glycerol and water:

* A. 1: 5: 2
B. 3: 3: 3
C. 1: 6: 3
D. 4: 1: 4
E. 1: 1: 8

16

The pharmacist should prepare an ointment that includes substances that are insoluble in the base or in water in an amount greater than 5%. How do you put them in the basics?

* A. Grind with a portion of the molten base
B. Grind with all unmelted base
C. Grind with part of the unmelted base
D. Pour from the family to the base fluid
E. Grind with an alcohol-water-glycerol mixture

17

The pharmacist prepared vaginal suppositories. What form of suppository did he prepare?

* A. Balls
B. Torpedoes are similar
C. cylindrical
D. The cones are similar
E. Sticks

18

The pharmacy received a prescription:
Rp.:Sulfuris praecipitati 2.0 Glycerini 5.0
Aquae purificate 100 ml
MDS rub in the scalp.
Specify the type of dosage form:
* A. Suspension
V. Emulsion
C. Solution
D. Colloidal solution
E. Navy solution

19

Pharmacist prepares ointment. In what sequence is it necessary to fuse substances?
* A. Squeal, Vaseline, Apricot Oil
B. Apricot oil, wax, petrolatum
C. Vaseline, wax, apricot oil
D. Squeal, apricot oil, petrolatum

20

Pharmacist prepares emulsion ointment. The substance is introduced into the ointment as a solution, regardless of concentration?
* A. Collargol.
V. Menthol
C. Sodium sulfacyl
D. Resorcinol
E. Potassium iodide

21

The pharmacist prepares rectal suppositories on a polyethylene oxide basis. Specify the fluid to be wiped off the suppository form:
* A. Vaseline oil
C. Ethyl alcohol

C. Soap alcohol
D. Water purified
E. Dimexide

22

The doctor discharged the suppository without specifying the reason. Specify the basis for the preparation of suppositories by pumping:

* A. Cocoa butter.
V. Lazupol
S. Lanol
D. Gelatin-glycerin
E. Butyrol

23

In the development of the process of obtaining the enzymes, of the drug is introduced into the stage of inclusion of the enzyme in the gel microcapsules. Is enzyme stability enhancer used at this stage?

* A. Immobilization
B. Lyophilization
C. Sterilization
D. Canning
E. Concentration

24

The doctor wrote out suppositories without specifying the reason. Specify the basis for the preparation of suppositories by pumping

* A. Cocoa butter
B. Lazupol
C. Lanol
D. Gelatin-glycerin
E. Butyrol

25

The pharmacist prepared the ointment as prescribed
Rp: Tannin 0.2 Lanolini 3.0 Vaseline 10.0
M.utf.ung.
DS Lubricate affected skin area
What method of tannin did he choose?

* A. Dissolved inlet, emulsified with lanolin anhydrous
B. Grind in a mortar according to Deryagin's rule with Vaseline oil

C. Dissolved in molten petroleum jelly
D. Grind in a mortar with alcohol and mix with the base
E. Dissolved in petroleum jelly

26

The pharmacist prepares suppositories by pouring.Why is the conversion factor from fatty base to gelatin -glycerin

* A. 1.21
B. 1,20
C. 1,31
D. 1,11
E. 1,25

27

To the lipophilicsuppository bases applies

* A. Alloys of hydrogenated fats
B. Polyethylene oxide base
C. Gelatin- glycerin base
D. Collagen base
E. Soap-glycerin base

28

The pharmacy produces suppositories on a gelatin-glycerol basis. How much of this base compared to fat should be used when:

* A. 1.21 times more
B. The same amount is required
C. 2.5 times more
D. 2 times more
E. 3 times more

29

In the manufacture of fat, linimentation as the basis of fatty oils are used. What oil did the pharmacist use if it was not indicated in the prescription.

* A. Sunflower oil
B. Vaseline
C. Fish oil
D. Sesame oil
E. Eucalyptus oil

30

In the manufacture of soft dosage forms use different types of bases.

Which of the following is hydrophilic
* A. Polyethylene oxide
B. Vaseline
C. Animal fat
D. hydrogenated fats
E. Petrolatum
31
The pharmacist prepared the medication as prescribed
Rp: Streptocides
Dermatoliana 1.0
Vaselini ad 10.0
Misce.Da.Signa. Apply to affected skin. Specify the type of dispersed system
* A. Ointment-suspension
B. Ointment solution
C. Ointment-emulsion
D. Ointment combined
E. Ointment-alloy
32
The pharmacist prepared the medication as prescribed
Rp.Dimedrols 0.3
Sol.Adrenaline hydrochloride gtts.
XXX
Lanolini 5.0
Vaseline 10.0
Misce, ut fiat ungventum
Yes
Ointment for the nose
Specify the rational route of administration of diphenhydramine:
* A. Dissolved in a solution of adrenaline, emulsified with lanolin aqueous
B. Dissolved in purified water, emulsified with lanolin anhydrous
C. Deriagin, dispersing with a portion of molten petroleum jelly
D. Triturated according to Deryagin's rule with Vaseline oil
E. Crushed with alcohol, emulsified with lanolin
33

The patient should prepare Vyshnevsky liniment. What substances can be used as a basis for liniment, guided by the requirements of regulatory documents

* A. Castor oil or fish oil

B. Sunflower or cottonseed oil

C. Camphor oil or glitter oil

D. Vaseline oil or petrolatum

E. Vaseline or lanolin aqueous

34

The patient needs to make rectal suppositories by pouring. Specify a hydrophilic base for the following suppositories:

* A. Polyethylene oxide

B. Cocoa butter

C. Butyrol

D. Lazupo

E. Vitepsol

35

Which group of excipients is polyvinyl alcohol allowed to use HFCs?

A. * Prolongers

B. Preservatives

C. PH regulators

D. Antioxidants

E. Isotonizing agents

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GLOSSARY OF TERMINOLOGY

Batch: A specific quantity of a drug or other material produced according to a single manufacturing order during the same cycle of manufacture and intended to have uniform character and quality, within specified limits.

Standard Term

Standard Terms for describing the pharmaceutical form of a medicinal product, the routes of administration and the containers used have been established by the European Pharmacopoeia Commission and are provided in a separate publication on Standard Terms.

Active substance

Equivalent terms: active ingredient, drug substance, medicinal substance, active pharmaceutical ingredient.

Vehicle

A vehicle is a carrier, composed of one or more excipients, for the active substance(s) in a liquid preparation.

Basis

A basis is a carrier, composed of one or more excipients, for the active substance(s) in semi-solid and solid preparations.

Conventional-release dosage forms Conventional-release dosage forms are preparations showing a release of the active substance(s) which is not deliberately modified by a special formulation design and/or manufacturing method. In the case of a solid dosage form, the dissolution profile of the active substance depends essentially on its intrinsic properties. Equivalent term: immediate-release dosage form.

Modified-release dosage forms

Modified-release dosage forms are preparations where the rate and/or place of release of the active substance(s) are different from that of a conventional-release dosage form administered by the same route. This deliberate modification is achieved by a special formulation design and/or manufacturing method. Modified-release dosage forms include prolonged-release, delayed-release and pulsatile-release dosage forms.

Prolonged-release dosage forms

Prolonged-release dosage forms are modified-release dosage forms showing a slower release of the active substance(s) than that of a conventional-release dosage form administered by the same route. The

prolonged-release is achieved by a special formulation design and/or manufacturing method.
Equivalent term: extended-release dosage form.

Delayed-release dosage forms

Delayed-release dosage forms are modified-release dosage forms showing a release of the active substance(s) which is delayed. The delayed-release is achieved by a special formulation design and/or manufacturing method. Delayed-release dosage forms include gastro-resistant preparations as defined in the general monographs on solid oral dosage forms.

Pulsatile-release dosage forms

Pulsatile-release dosage forms are modified-release dosage forms showing a sequential release of the active substance(s). The sequential release is achieved by a special formulation design and/or manufacturing method.

Large-volume parenteral

Infusions and injections are supplied in containers with a nominal content of more than 100 ml.

Small-volume parenterals

Infusions and injections are supplied in containers with a nominal content of 100 ml or less.

Drug Product: A drug product is a finished dosage form (e.g., tablet and capsule) that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients. A solid oral dosage form includes but is not limited to tablets, chewable tablets, enteric-coated tablets, capsules, caplets, encapsulated beads, and gelcaps.

Drug Substance: An active ingredient that is intended to furnish pharmacological activity or other direct effects in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or to affect the structure of any function of the human body, but does not include intermediates used in the synthesis of such ingredient.

Enteric Coated: Intended to delay the release of the drug (or drugs) until the dosage form has passed through the stomach. Enteric-coated products are delayed release dosage forms.

Equipment: Automated or nonautomated, mechanical or nonmechanical equipment used to produce the drug product, including equipment used to package the drug product.

Extended-Release: Extended-release products are formulated to make the drug available over an extended period after ingestion. This allows a reduction in dosing frequency compared to a drug presented as a conventional dosage form (e.g., as a solution or an immediate release dosage form).

Formulation: A listing of the ingredients and composition of the dosage form.

Immediate Release: This allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug.

Types of Extract

The Liquid Extract is the strongest type of plant liquid made, its ratio, of the-plant material to solvent is 1:1, i.e., 1 gram crude drug represents 1 ml of the liquid extract. For technical reasons, it may only be further concentrated by evaporation of the solvent. Occasionally a 1:2 preparation, i.e., 1 g crude drug equals 2 ml liquid is called an extract, this is incorrect and leads to confusion. When the term extract is used here, it means a 1:1 preparation.

The Tincture is the most common form of plant liquid. An official definition of a tincture is that it has a drug/solvent ratio of 1:4 and that the solvent is a minimum of 45% by volume. There are some difficulties with that definition because there are strong tinctures, i.e., 1:2 or 1:3, or they may go from 1:5 through 1:10. International protocol on potent plant drugs, e.g., Belladonna, Digitalis, Strophanthus etc., are agreed upon 1:10. The international protocol was established for obvious reasons. Preparations above 1:10 are little more than preserved concentrated infusions.

The Essential Oils represent a fraction of 1% of the total plant constituents and are not representative of a plant's therapeutic range. They are undoubtedly the finest natural bactericide, that because of their potency can be dangerous in the wrong hands. Therefore, if taken internally they can be extremely toxic and if used without dilution externally, the result will be damage to dermal or mucous tissue.

The Expressed Plant Juices enjoyed popularity in the early years of the 20th century but were gradually abandoned because of their limitations. They are brisk and vigorous in action; this may be attributed to the live enzyme content and as such bear comparison with fresh fruit and

vegetable juices, however strict dosage restraints must be adopted otherwise harm may result. The preserved juices are problematic.
The Concentrated Infusions and Decoctions were prepared with water as the solvent. If taken in that form they are classed as retention (recent) or they are preserved with alcohol 20%.
The Pasty or Dry Extracts are prepared from liquid extracts by evaporation. They must be prepared with extreme care lest irremediable damage occurs. There are three types;
(1) Soft. (2) Semi-soft. (3) Dry.
They are the basis of pills and ointments.
Dry Yield Converted to Liquid Yield
On the assumption of 100 kg of dried material, a liquid extract will yield 100 litres of extract.
On the same amount of dried material, 1 in 4 tinctures will yield 400 litres of the tincture. A Homeopathic mother tincture is 1 in 10. (There are a few odd exceptions). Therefore, the original 100 kg of dried material will yield 1000 litres of the mother tincture. It may be seen that the original 100 kg of dried material has suddenly started to be commercially viable.

THE ENGLISH-UKRAINIAN VOCABULARY OF TERMINOLOGY

airbubblenucleation-заповітрювання(виникненнягазовихпузирів)
anginapectoris-серцеванедостатність
biocompatibility-біосумісний
buccal-той,щовідноситьсядоротаабощоки
casting-лиття
crosslinking-перехреснозшитий
extruded-пресований;видавлений
fluidization-псевдозрідження
injectable-ін'єкційний
massexchange,
masstrasfer–масообмін
mass-transfer-масопереніс
melting-плавлення

molded-формований
mullercontainer-мюлерівськабочка
multistagely-багатостадійно
Permeation,penetration-проникнення
predesigned-запланований
Prolonged-прил.пролонгований,довгий
Rate-preprogrammed-зпрограмованоюшвидкістюrotary-pulsatingd
evice-роторно-пульсаційнийапарат
Site-targeting-доставкадомісця
semifinisheditems-напівпродукти
semipermeable-напівпроникний
swell-набрякати
transdermally-трансдермально,підшкіру
trans-mucosal-черезслизовуоболонку
vortical-вихровий
wall–пристінний

THE UKRAINIAN-ENGLISH VOCABULARY OF TERMINOLOGY

багатостадійно-multistagely
біосумісний-biocompatibility
вихровий–vertical, vortex
доставкадомісця-Site-targeting
запланований-predesigned
заповітрювання(виникненнягазовихпузирів)-airbubblenucleation
зпрограмованоюшвидкістю-Rate-preprogrammed
ін'єкційний-injectable
лиття-casting
масообмін-massexchange,masstransfer
масопереніс-mass-transfer
мюлерівськабочка-mullercontainer
набрякати-swell
напівпродукти-semifinisheditems
напівпроникний-semipermeable
перехреснозшитий-crosslinking
плавлення-melting
пролонгований,довгий-Prolonged
проникненйя-Permeation,penetration

пресований;видавлений-extruded
пристінний-wall
псевдозрідження-fluidization
роторно-пульсаційнийапарат-rotary-pulsatingdevice
серцеванедостатність-anginapectoris
той,щовідноситьсядоротаабощоки-buccal
трансдермально,підшкіру-transdermally
формований-molded
черезслизовуоболонку-trans-mucosal