



Secundum Artem

Current & Practical Compounding
Information for the Pharmacist

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Compounding Foams

GOALS AND OBJECTIVES

Goal: To provide information on the use of foam dosage forms and pharmacists ability to extemporaneously compound them.

Objectives: After reading and studying the article, the reader will be able to:

1. Discuss the rationale and advantages of using foams,
2. Differentiate between the various types and structures of foams,
3. List the various types of ingredients and give examples of each and
4. Describe the preparation of pharmaceutical foams.

INTRODUCTION

Foams, along with emulsions, are colloids and are composed of two or three distinct phases; normally a hydrophilic liquid continuous phase with a foaming agent where a gaseous dispersion phase is distributed. A third, hydrophobic dispersed phase, may also be involved.

A foam is a material and foaming is a process; both involve the presence of a gas phase encapsulated within either a liquid or solid phase. Foaming is a dynamic and complex phenomenon that involves scientific and engineering principles but are often difficult to control.

There are basically two types of foams: static and dynamic. Static foam examples are marshmallows, Styrofoam™*, foam seats/cushions, etc; dynamic foams include cakes, bread, cosmetics, pharmaceuticals, etc. Foams are very attractive as a drug delivery system and are becoming more popular for a number of reasons, including those characteristics listed in Table 1.

Rapid evaporation of foam ingredients can influence the rate of drug penetration into the skin as the rate of drug penetration is proportional to its degree of saturation in the vehicle at the vehicle-skin interface. Also, due to evaporation of the solvent, there is a "cooling effect" on the skin, especially inflamed skin. Patients generally will prefer a foam over an ointment, cream or solution.

*Styrofoam™ is a registered trademark of Dow Chemical Company

Table 1: Desirable Characteristics and Advantages of Foams

- Minimal or lack of greasiness, oiliness or tackiness
- Creates a pleasant feeling after application
- Easily used on hair-bearing skin
- Easily applied to mucosal areas, to sensitive or to highly inflamed skin
- Spread easily on a skin surface
- Leaves minimal shiny residual look
- Absorb and penetrate quickly without leaving any greasy residue
- Substantially absorbed following rubbing onto the skin

DEFINITIONS AND BACKGROUND

A foam is an emulsion packaged in a pressurized aerosol container that has a fluffy, semisolid consistency when dispensed. The European Pharmacopeia describes a "medicated foam" as a formulation, consisting of a large amount of gas dispersed in a liquid phase. The USP lists a "foam aerosol" as a subcategory of the aerosols.

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FOAM STRUCTURE

Foams are three-dimensional agglomerations of gas bubbles separated from each other by thin sections (film, lamellae) of a host medium. A foam is a dispersion of gas in a liquid or a solid and the volume fraction of gas in the foam is usually between 0.5 and 0.9. The size of the foam bubbles is mostly between 0.1 and 3 mm. Foams can be liquid or solid. Solid foams can be generated when the liquid phase is changed into either a gel or a solid after foam formation and are also called dry foams, xerogels or sponges; these can be used to cover exuding wounds, etc. and may contain disinfecting agents, antibiotics or steroids. Collagen or gelatin sponges can absorb a lot of fluids (ichor) because of their high capillarity.

A "liquid foam" is in an intermediate state with a tendency to break down at some point. For example, if an emulsion is administered to the skin as a foam, it will return to an emulsion state after the air bubbles have separated.

Foams are thermodynamically and mechanically unstable systems; they are characterized by a very large interface which has a tendency to reduce itself. Foams are "elastic systems" and the entrapped gas phase can be compressed. A successful foam requires the formation, growth and stabilization of the gas bubbles in the reacting medium.

The bubbles in a foam can be more or less homogeneous and vary in size and shape ranging from almost spherical to irregular polyhedral, depending on how the foam was generated and the incorporated excipients. Other parameters include the nature and concentration of the foaming agent, viscosity of the liquid phase, temperature and pH of the system: all these can affect the foam structure.

The thin layer of the continuous liquid phase or film separating the faces of two bubbles are called lamellae and their thickness can vary between 10 nm and 1 micrometer. The liquid is "fixed" by the molecules of the foaming agent and this fixation is critical because if it was not fixed, the liquid would drain due to gravity leaving the air bubbles without a wall and result in breaking of the foam. Even with a good foaming agent, the liquid tends to eventually gravimetrically drain down, resulting in a thinner film or lamellae and a breaking of the foam.

TYPES OF FOAMS

Quick breaking-foams are thermally unstable and collapse upon exposure to skin temperature. A typical example is the hydroalcoholic foams.

Lathers-soapy foams are stable when formed and increase in volume when rubbed (shaving foam).

Breakable-foams are stable at skin temperature but collapse and spread easily when a mild shear force is applied. These are very good for dermatological and mucosal tissue application.

Aqueous-foams contain a large percentage of water and may be alcohol-free.

Hydroalcoholic-foams contain varying percentages of alcohol.

COMPOSITION

Pure liquids do not foam but require the presence of a foaming agent. There are three stages of foam generation:

1. Solution of the foaming agent.
2. Emulsification of the gas (the solution starts to incorporate air, at lower volume fractions air bubbles do not have contact with each other; there is no influence on bubble geometry.)

3. Foam (polyhedral foam, air bubbles have contact with each other through lamellae and their spherical geometry is altered.)

PHARMACEUTICAL FOAM COMPOSITIONS

Foam compositions generally consist of hydrophilic and/or hydrophobic solvents or liquids, emollients, co-solvents, foaming agents, gelling agents, foam adjuvants and water.

Hydrophilic Solvents

Water is a primary solvent in most foam systems. The creation of a foamable composition with low water content is not easy and usually requires very high concentrations of a foaming surfactant system, which may comprise a high proportion of ionic surfactants. Examples of hydrophilic solvents include glycerin, propylene glycol, hexylene glycol, diethylene glycol, terpenes, di-terpenes, limonene, terpeneol, l-menthol, dioxolane, ethylene glycol, dimethylsulfoxide (DMSO), dimethylformamide, dimethylacetamide, azone, myristyl alcohol, lauryl alcohol, lauric acid, caprylic acid and polyethylene glycols.

Hydrophobic Solvents

Hydrophobic solvents are described as materials with a solubility in purified water at room temperature of less than about 1 g per 1000 mL or less and are liquid at room temperature. Examples include mineral oil, triglyceride oil, olive oil, corn oil, soybean oil, canola oil, cottonseed oil, coconut oil, sesame oil, sunflower oil, borage seed oil, cod liver oil, salmon oil, flaxseed oil, wheat germ oil, evening primrose oils, omega-3 and omega-6 fatty acids, linoleic acid, linolenic acid, gamma-linoleic acid, eicosapentaenoic acid, docosahexaenoic acid and some essential oils.

Emollients

Emollients are agents that can be used to soften the skin or soothe irritated skin or mucous membranes. Example emollients include hexylene glycol, propylene glycol, isostearic acid derivatives, isopropyl palmitate, isopropyl isostearate, diisopropyl adipate, diisopropyl dimerate, maleated soybean oil, octyl palmitate, cetyl lactate, cetyl ricinoleate, tocopheryl acetate, acetylated lanolin alcohol, cetyl acetate, phenyl trimethicone, glyceryl oleate, tocopheryl linoleate, wheat germ glycerides, myristyl myristate, triisocetyl citrate, octyl dodecanol, octyl hydroxystearate and mixtures.

Silicone Oil

Silicone oils are known for their skin protective properties and may be used as a hydrophobic solvent. Generally, examples are silicone oil at a 2-5% concentration.

Foaming Agents

Foaming agents are amphiphilic substances. The hydrophilic part relates to their solubility in water. The hydrophobic part arranges to minimize that portion contact with the water and leads to their orientation at the air-water interface and the formation of micelles in the bulk of the liquid phase. Foaming agents may include many different surface-active agents, including anionic, cationic, non-ionic, switterionic, amphoteric and ampholytic surfactants or combinations.

When a foaming agent is adsorbed into the air-water interface, the surface tension of water is lowered and the surface pressure is increased. For stability of the foam, the concentration of foaming agent in an adsorbed layer is most important. In a homologous series of foaming agents, the maximum foaming ability occurs at a concentration about equal to the critical micelle concentration. The combination of two different foaming agents may or may not lead to increased foam stability.

During foam formation, the concentration of the foaming agent in the bulk phase will decrease with an increase of the newly created surface area; the higher the volume fraction and the smaller the air bubbles, the larger the surface area will be. To ensure a rapid diffusion of a foaming agent to the surface, a high foaming agent concentration and a low viscosity of the liquid phase are needed.

Example foaming agents include sorbitan laurate, sorbitan palmitate, laureth-4, polyglyceryl-4 isostearate, lecithin, polyoxyethylene (20) sorbitan monostearate (Tween 60), polyoxyethylene (2) sorbitan monooleate (Tween 80), Myrj 45, Myrj 49, Myrj 59, Brij 38, Brij 52, Brij 56, sorbitan monolaurate, isoceteth-20, sodium lauryl sulfate, triethanolamine lauryl sulfate and others.

Foam Adjuvants

Foam adjuvants are included to improve the stability and reduce the specific gravity of the foamed composition; they may increase the foaming capacity of the surfactants. They can include fatty alcohols, fatty acids and their mixtures. Examples include cetyl alcohol, stearyl alcohol, oleyl alcohol, arachidyl alcohol, behenyl alcohol, hexadecanoic acid, stearic acid, arachidic acid, behenic acid, and octacosanoic acid.

Gelling Agents

Gelling agents are present for the creation and stabilization of the foam, having a fine bubble structure so that it does not readily collapse upon release. They are usually included at less than 1% of the composition and will aid in increasing viscosity. Examples include locust bean gum, sodium alginate, sodium caseinate, egg albumin, gelatin agar, carrageenan gum, xanthan gum, quince seed extract, tragacanth gum, starch, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxyl propylmethyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, guar gum, hydroxypropyl guar gum, polymethacrylic acid polymers, acrylic acid/ethyl acrylate copolymers and carboxyvinyl polymers.

Preparation of Foams

Foams are produced by supersaturating a liquid phase with gas. A typical foaming process involves (1) dissolution of the foaming agent, (2) bubble nucleation, (3) bubble growth, and (4) stabilization. Methods to achieve this include whipping, shaking, bubbling, pressurized aerosols and aerospray foam pumps. Of these, pharmacists generally have access to all but pressurized aerosol preparations.

Whipping, also called beating, is accomplished with different devices that agitate a liquid in order to form an interface with a gas phase. The volume of air incorporated usually increases with an increase in the beating intensity. High viscosity liquids do not produce stable foams. During whipping, each air bubble undergoes severe mechanical stress and a more rapid coalescence happens during foam generation than in a standing foam. The mechanical stress produces smaller bubbles from larger ones. This technique is widely used in the food industry (whip cream, desserts, toppings).

Shaking is rarely used as it produces low foam volumes after a long generation time. The resulting foam is based upon the frequency and amplitude of shaking, the volume and shape of the container and the volume and viscosity of the liquid.

Bubbling is the injection of gas through narrow openings into a foamable liquid and is reproducible and gives uniform bubble sizes. The foam volume produced using this technique is dependent upon the total amount of foaming agent and the solution being bubbled.

Pressurized aerosols include both two-phase and three-phase aerosol foams. In the two-phase system, the liquified propellant is dissolved in the solution of a foaming agent under pressure. In the three-phase system, the propellant is dissolved in a lipid phase, which is emulsified with a water phase using an emulsifier. The foaming agent can also act as an emulsifier. The third phase is the vapor phase of the propellant over the emulsion. Both two- and three-phase systems should be shaken prior to use. In these systems, the propellants with low boiling points evaporate rapidly leading to immediate foam generation. Water is most commonly used as a solvent in foam aerosols, as well as ethanol and isopropanol. Examples here are shaving foam, hair mousse, aerosol shampoo, aerosol hand creams etc. The most common propellants include n-butane, isobutene, n-propane or mixtures of these. Their concentration is typically in the range of 3-12%.

Gas generation method can use effervescent formulations for gas production. When the ingredients come into contact with water or mucosal secretions, gas is generated resulting in foam production; this is used in vaginal and rectal foams and tablets.

Airspray foam pumps create foam without the use of gas propellants. It allows mixing of the liquid with air, resulting in foam generation. These are relatively simple systems to use and the viscosity of the liquids may need to be altered for greater efficiency. In fact, one relatively simple method is to dilute a lotion vehicle with preserved water, add the API and package in the pump system. This device enables compounding pharmacists to extemporaneously prepare foamed dosage forms.

Factors Altering Foams

A foam booster is a substance that enhances foam formation and includes fatty acid alcohol amides, e.g. oleic acid diethanol amide, coco fatty acid diethanol amide, polycarboxylic acid poly diethanol amide; these are normally used at a 5% concentration; higher concentrations may become irritating. The addition of some polymers (cellulose derivatives, xanthan gum, etc.) can be used to increase foam stability.

Foam Destroyers are agents that will decrease the stability of a foam. Foam destroyers include small oil droplets that spread on the foam lamellae, thin the lamellae, and result in breakage. These include oils, alcohols and organic solvents that are normally poorly soluble in water. They orient themselves at the surface leading to an increase in surface pressure and a reduction of the elasticity of the surface film produced by the foaming agent; this results in rupture of the lamella or film. Foam inhibitors generally have an affinity for the interface in preference to the foaming agents and prevent foam generation. Foam inhibitors include some electrolytes as well as poorly wettable solid particles.

SCALES FOR FOAM QUALITY

Foams can vary as to their quality. An approximate scale used for comparison purposes includes their appearance, bubble structure and spreadability. The following has been used to subjectively describe foams:

E = Excellent: very rich and creamy in appearance, does not show any bubble structure or shows a very fine (small) bubble structure.

G = Good: rich and creamy in appearance, very small bubble size, "dulls" more rapidly than an excellent foam.

FG = Fairly Good: a moderate amount of creaminess noticeable, bubble structure is noticeable.

F = Fair: very little creaminess noticeable, larger bubble structure than a "fairly good" foam.

P = Poor: no creaminess noticeable, large bubble structure.

VP = Very Poor: dry foam, large very dull bubbles, difficult to spread on the skin.

STABILIZATION AND STABILITY

Foam stability is oftentimes difficult to predict. Although many studies have been conducted, it has been found to be very difficult to develop a general theory related to foam stability since both dynamic and static factors are involved. Basically, if a film or lamellae between two bubbles ruptures, the bubbles coalesce. This results because a number of processes may be occurring, including Ostwald ripening, gravitational separation (creaming, bubbles rising, and drainage) and Brownian motion. When bubbles are formed, changes occur. The pressure in smaller bubbles is greater than larger bubbles with resulting dissolving of the smaller bubbles into larger ones by diffusion of the gas (air). Also, with a difference in the density between the phases, gravitational and capillary forces cause a flow of the continuous liquid around the air bubbles resulting in the air bubbles moving towards the top and the liquid flowing downward. This gradient can be stabilized with the adsorption of a foaming agent from the bulk solution.

Foams with a higher gas volume fraction are more stable as liquid drainage and creaming is delayed. Also, higher viscosities can delay the drainage and creaming activity. Arabic gum, methylcellulose and similar hydrophilic materials of high molecular weight will tend to increase foam stability due to increased viscosity. Temperature also can affect stability by altering bulk viscosity. The use of macromolecules that orient at the surface can provide steric stabilization and hinder the coalescence of bubbles. The addition of any electrolytes to a foam will generally break the foam as the aqueous film has a greater affinity for the electrolytes than the gas and results in coalescence.

PHARMACEUTICAL FOAMS

Aerosol foams containing numerous drugs are commercially available. They are generally water miscible and nongreasy. Table 2 lists a number of commercial foams; some of which are under development. They include those that are applied topically/dermally, vaginally, rectally and possibly nasally. An example of a commercial product is Cortifoam that contains hydrocortisone acetate 10% in a base containing propylene glycol, emulsifying wax, polyoxyethylene-10-stearyl ether, cetyl alcohol, methylparaben, propylparaben, trolamine, purified water and inert propellants.

Table 2: Example Foams Under Development

Active Ingredient	Concentration	Indications	Category
Acyclovir	5%	Genital herpes, labial herpes	Dermatological
Ammonium lactate	12%	Dry, scaly skin	Dermatological
Betamethasone valerate	0.12%	Psoriasis, Atopic dermatitis	Dermatological
Diclofenac	1%	Osteoarthritis, joint/back pain	Dermatological
Diclofenac	3%	Actinic keratosis	Dermatological
Diethyl toluamide	25%	Protection from insect bites	Dermatological
Mupirocin	--	Impetigo, Infections	Dermatological
NSAID	--	Topical dermatitis	Dermatological
Permethrin	1%	Lice, Scabies	Dermatological
Terbinafine	2%	Dermal mycoses	Dermatological
Urea	10, 20, 40%	Dry, scaly skin	Dermatological
Zinc oxide	--	Diaper rash	Cosmetic

MISCELLANEOUS

The actual first entry into the “rapidly dissolving tablet” entry was the Zydys delivery system prepared by foaming a mixture of gelatin, sugar or sugars, drug and other components. The foam is filled into a mold and the product lyophilized. The resulting very porous tablet is one of the most rapidly disintegrating tablet on the market.

Other developmental approaches involved preparing a “foam blank” and then adding a solution of the drug to the “blank” and allowing the solvent to evaporate. This process is called “post-loading” and can provide numerous advantages, especially to a compounding pharmacist.

EXAMPLE FORMULAS

Rx Effervescent Foam Breakup Tablet

Sucrose	3 g
Citric acid	120 mg
Sodium bicarbonate	100 mg
Mannitol	3 g
PEG 3350	1 g
Flavor	qs

Weigh the ingredients, place in a mortar and mix well. Place the required quantity of powder into molds and set on sieve or other “holder”. Heat at 90° C for 10 minutes, remove to a refrigerator for 10 minutes, then to room temperature. Package and label.

Rx Effervescent (Foaming) Metoclopramide and Aspirin Granules

Metoclopramide HCl	236 mg (Equiv to 200 mg base)
Aspirin	6 g
Citric acid (Hydrous)	49.8 g
Sodium bicarbonate	44 g

Weigh and thoroughly mix the powders. Place in a flat bottom glass container (Pyrex™** cake or similar) and spread out with a flat spatula. Place in a 300° C oven and monitor carefully. When the citric acid begins to lose its water, the mass will stick together and the powder should be gently moved around to form granules. After the water has been released and the powder formed into small granules, sieve through a #8 or #10 sieve. Cool to room temperature and package in a tight container. A 5 g measuring device can be used to measure the dose of granules. Package and label. When ready to administer, place the granules in a small glass of water where they will effervesce/foam. When the effervescence slows down, the mixture can then be taken.

Rx Iodine Foam in Airspray Foam Pump

Iodine	1%
Purified water	64.3%
Glycofuroil	30%
Stearyl alcohol	1%
Sucrose stearate	1%
Sodium lauryl sulfate	1%
Cocamidopropyl betaine	0.5%
Hydroxypropyl methylcellulose	0.8%
Xanthan gum	0.4%

Dissolve the iodine in a mixture of glycofuroil and stearyl alcohol, heating to about 60° C until homogenous. Disperse the HPMC in 1/3 the portion of water preheated to 80° C. Add the sucrose stearate and mix well. Using the remaining 2/3 of water at room temperature, add the xanthan gum and sodium lauryl

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sulfate and cocamidopropyl betaine mixing continuously for 15 minutes under vigorous stirring. Add the iodine mixture carefully to the aqueous mixture and stir for an additional 5 minutes for complete homogeneity. Cool to room temperature, place into bottles and label.

Container source: Rexam Airspray, 3768 Park Central Blvd, North Pompano Beach, FL 33064

Rx Foamable Carrier Formed by Whipping/Shaking

Propylene glycol	82%
Laureth-4	2%
Glyceryl stearate	2%
PEG-100 stearate	2%
PEG 4000	10%
Hydroxypropyl cellulose	2%

Weigh/measure the ingredients. Warm the propylene glycol to about 50° C and dissolve the ingredients. Cool to room temperature. Agitate/whip the solution until it foams and the desired bubble size is obtained. Package and label.

Rx Drug X mg Mini-Marshmallow

Drug	x
Stevia	200 mg
Peppermint/Wintergreen blend	qs
Alcohol 95%	qs 100 mL
Mini-Marshmallows	qs

Dissolve the drug, stevia and peppermint/wintergreen blend in sufficient alcohol to volume. Prepare the solution such that the required amount of drug is in about 50-100 microliter of solution. Using a calibrated micropipette, deliver the required volume of drug solution to each individual mini-marshmallow and allow to air-dry. Package and label. As an option, each mini-marshmallow can be halved prior to dosing.

Diclofenac Foam with Aerosol propellants

Mineral oil	6.00%
Isopropyl myristate	6.00%
Stearyl alcohol	1.00%
Xanthan gum	0.30%
Methocel K100M	0.30%
Tween 80	1.00%
Myrj 49	3.00%
Cocamidopropyl betaine	0.50%
Diclofenac sodium	1.0%
Methylparaben	200 mg
Propylparaben	50 mg
Propellant	8.00%
Purified water	qs 100.00%

1. Aqueous Phase: Dissolve the xanthan gum, the Methocel K100M, Tween 80, Myrj 49, cocamidopropyl betaine, methyl paraben and propylparaben in water, with agitation. The solution is warmed to 50-70° C.
2. Hydrophobic Phase: Heat the isopropyl myristate, stearyl alcohol and mineral oil together to the same temperature.
3. Add the warm hydrophobic phase into the warm aqueous phase with agitation, followed by homogenization. Allow the mixture to cool to room temperature. Add the diclofenac sodium and then add to an aerosol container along with the propellant and seal. Label.

ERRATUM

Secundum Artem Volume 16 Number 3. Reference number 4 should be Skillman KL, Caruthers RL, Johnson CE. Stability of an extemporaneously prepared clopidogrel oral suspension. Am J Health-Syst Pharm. 2010;67(7):559-561.