Pharmaceutical Foam Drug Delivery System: General Considerations

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ABSTRACT

A foam composition mainly comprises of a major amount of water, least quantity of foam stabilizing agent and emulsifying surfactant, water soluble polymer and water immiscible liquefied gas foaming agent. Pharmaceutical foam drug delivery is more successful in dermatology because of ease of application, good spreadability than any other topical dosage form, less dense and no any greasy or sticky residue remaining after application on skin. Surfactant is the key ingredient in development of foam drug delivery system. Foam is used to deliver various categories such as anti-inflammatory, anaesthetics, protectives, antifungal, skin emollients, antiseptics, antipruritics etc. Foam drug delivery system increase the effectiveness of therapy by instant absorption and improving patient compliance hence plays important role in skin care market. In the present article an insight into foam drug delivery system is provided giving emphasis on foam properties, evaluation, and application of foam drug delivery system.

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INTRODUCTION

The most common dosage forms used in dermatological application are solutions, suspensions, creams, gels, ointments, and lotions. Topical drug delivery system remains the most common method for providing dermatologic therapy. It is associated with enhanced overall safety and minimal risk of systemic exposure and associated side effects. However, effective topical drug delivery presents challenge that epidermal barrier is supposed to prevent entry of chemicals and makes the passage of topically applied drugs difficult in deeper layer of skin and hence drug that gets through the stratum corneum is very low. So there scientist need to develop topical drug delivery systems that efficiently bypasses the barrier properties without significantly damaging the barrier. Foam drug delivery permit rapid diffusion of drugs into the stratum corneum or deeper skin layers and hence suitable for dermatological disorders.

Recently vehicle delivery system that is growing with popularity is foam drug delivery system. Foam is, quite simply, a dispersion of gas in a liquid or solid. While solid or dry foams exist within the medical marketplace as dressings. Foams are colloids “composed of two or three distinct phases: a hydrophilic liquid continuous phase with a foaming agent, throughout which a gaseous dispersion phase is distributed, there may be a third hydrophobic dispersed phase.” Pure liquids will not form foam, therefore foaming and bodying agents are used for generation and stabilization of foams. The type and amount of foaming agent will influence the stability of the foam and its density. Most pharmaceutical foams are essentially created at the time of use and exist only for a concise duration. The use of foam drug delivery in dermatological applications was first reported in 1977 by Woodward and Berry, who studied the therapeutic benefit of betamethasone benzoate in hydroalcoholic quick breaking foam in comparison with semi-solid dosage form. Their study revealed high clinical efficacy in the treatment of psoriasis and excellent acceptability by patients. The successful acceptance of foam drug delivery in dermatological applications is being followed by the emergence of cosmetic and cosmeceutical foams, which likely could constitute an important segment in the skin care marketplace. Foam has become a prominent delivery system for topical active agents in dermatology. Its platform provides an ease of application alternative to creams and ointments. Foam delivery is useful in that it easily spreads over large surface areas and it does not leave a greasy, sticky or oily film on the skin after application. Most pharmaceutical foams are liquid dosage forms, because that is how they exist in the can; the foam essentially is created at the time of application and exists only for a short duration. Simple, safe and effective, foam is suitable for dermatological and gynaecological applications due to the fact that it is, Unique: High patient usability, good spreadability, maximum effectiveness, improved compliance. Versatile: The foam vehicles are compatible with multiple active ingredients such as small and large molecules, water sensitive drugs, suspension, water and oil soluble agents, air and light sensitive drugs.

Advantages of foam drug delivery

- Comparable cost than other topical formulation types.
- High level of patient satisfaction.
- Foam formulations offer good spreadability and instant absorption; and extensive rubbing onto the skin is not required.
- Ease of application to hair bearing and other skin also reduces need to manipulate inflamed skin.
- The superior usability profile of foam is particularly precious in the treatment dermatological disorders, which involves application to large and sensitive skin surfaces.
- Focus group studies revealed that most users prefer foam over creams and ointments.
- May incorporate barrier repairing and/or emollient ingredients in formulation [11].

Types of Foam

Foam can be classified as aqueous stable foam, non- aqueous stable foam, thermal foams and quick breaking foam, copious foam, billowing foam, lacy foam, emollient foam [6,12,13].

Thermal foam: Drug is dispensed in the form of foam upon application of heat.

Copious foam: It refers to small bubbles with rich, dense and tight foam which is strong enough to resist deformation.

Bilowing foam: It is the opposite to that of copious foam. The bubbles in such a foam are large and the foam may get collapse easily.

Lacy foam: It is similar to billowing foam. A lacy foam lacks the tightness and richness and. It is dry foam in which the bubbles are separated from each other by very thin aqueous membranes with no mechanical strength.

Emollient foam: It is another form of foam which is based on oil-in-water (o/w) or water-in-oil (w/o) emulsions, therefore possessing vehicle properties similar to traditional creams.

Foam Properties

Foams are unstable and hence get collapse to liquid form having lowest energy state. Strong adsorption of a surface active agent at bubble walls opposes this collapse. Adsorption occurs because lyophobic part of surfactant molecule tries to escape from the solvent by moving to the liquid surface and orienting away from the liquid while lyophilic part remains in the liquid. To produce foam thick, long lasting one should consider some properties such as,

Surface viscosity- By cross-linking surfactant molecule on bubble surface via hydrogen bonding produces thick, more stable, long lasting foam and also slowdown the drainage of liquid from foam.

Surface elasticity- In this, self heal effect, in which thin spots in the bubble (points of likely bursting) can be repaired due to surface elasticity. If the rate of movement of surfactant molecule is fast then weak spots may not be repaired because surfactant molecule in the bulk liquid between bubble walls may rich the weak spot in the film before surface transport operates.
Bulk viscosity: It gives thick, long lasting foam by decreasing drainage rate.

Electrical repulsion: It prevents further thinning of bubbles which is caused by anionic or cationic surfactants.

Gas diffusion: Freshly generated foam having different size in which, small sized bubble get diffused into larger ones. Here adsorbed surfactant to the bubble walls mainly reduces gas diffusion [9].

Surfactants plays important role in lowering the surface tension of liquids and hence liquids can be mix with gases to generate foams. Foam mainly consists of two phase system where gas cells are separated by thin layer of liquid films. [8] Surfactants contribute in foam generation, is mainly due to their orientation at the air-water interface. The polar heads of surfactants are immersed in the polar aqueous medium and the non-polar tails are facing toward the gaseous phase. These polar heads are the sites for the formation of association of water molecules. Shape and nature of the surfactants are important factors in foam production. The critical packing parameter (CPP) provides a relationship between shape and foam production of a surfactant, by considering the shape of foam producing amphiphiles as a cone or truncated cone, the value of its CPP should be equal or less than 0.5 in order to generate foam. Sulphated anionic surfactants can provide desirable foam properties in shaving products. However, surfactant blends have been found to be good substitutes for sulphated anionic surfactants. Surfactant blends comprise of two main compounds:

1) A primary foaming agent: It consists of an amphoteric surfactant and a non-ionic surfactant and their mixture.

2) An acyl actylates: It enhances foam volume and provides spherical foam.

Use of surfactant blends is advantageous because it provides rich and stable foam and they enhances viscosity and mildness of foam to the skin [13].

Surfactants are usually lower the surface tension of the liquid to create and stabilize foam. Foam formation is a dynamic process, and foam is thermodynamically unstable. Foam quality and stability are two important parameters used for foam characterization. Foam quality is the percentage of gas volume in the total foam volume. Foam stability is generally measured by the volume or height change of foam in a container over time. The stability of all foams decreased with increasing quality. Foam stability generally increases when the surfactant concentration in the foaming solution increases up to 1.5%. The decrease in pH of the foaming solution decreased the foam stability within a tested range between pH 11 and 7.5 [8].

Water is the most commonly used solvent in aerosol foams while ethanol and isopropanol are used less frequently. It is established that alcohols in a foam formulation can have a temporary permeabilizing effect on the skin prior to their evaporation. Foams in general may be associated with enhanced drug penetration due to their unique nature. As volatile ingredients and co-solvents dissipate, a supersaturated drug formulation is transiently formed at the application site, and thermodynamic forces help drive active drug diffusion into the cell. A saturated solution may yield maximum concentration gradient and maximum thermodynamic activities, both of which facilitates rapid and efficient drug delivery and thus allow foams to potentially serve as an ideal topical drug delivery system. In addition to foaming agents, the product dispenser is essential to the creation of topical foam.

The ethanolic foam vehicles are thermolabile, dissolving at body temperature which provides good spreadability and cosmetic elegance here enhanced drug delivery associated with foams does not depend solely on alcohol content. After evaporation of the alcohol and propellants foam creates super saturation which provides a driving force for drug delivery into the skin. The first widely successful topical foam formulations available in the dermatological application were hydroethanolic foam formulations of corticosteroids. Due to the alcohol content of hydroethanolic foams, these have been associated with a potential for transient stinging or burning upon application, which may limit their success for some patients. However, it is evident that any temporary application site stinging/burning does not hinder treatment for most patients [11].
Pharmaceutical foams are pressurized dosage forms which contain one or more active pharmaceutical ingredients that, upon valve actuation, emit a fine dispersion of liquid and/or solid material in a gaseous medium from container. Mostly foam used in pharmacological applications is aerosol foams, which typically come in two or three phase system. Two phase systems consist of a solution comprises of solvent, foaming agent, foam stabilizer and a gas phase comprises of propellant vapor while three phase systems, typically the propellant is solved with a lipid phase that is emulsified in a water phase. A foaming agent and emulsifier are needed in least quantity. The vapour phase is the third. Emollient oil-in-water (o/w) or water-in-oil (w/o) foams may contain no alcohol but may have lipid concentrations up to 75 percent. Waterless foams have also been developed that feature hydrophilic solvents, such as polyethylene glycol (PEG), propylene glycol, or glycerine. In aerosols commonly used propellants include n-butane, isobutene, n-propane, or mixtures of these. These are liquefied under normal pressure, comprise 3-12% of the concentration of the initial formulation. Otherwise, one can use compressed air as an immediately evaporating propellant. Sometimes, along with air, secondary propellants can be used such as n-pentane, iso-pentane or isobutene that have delayed evaporation rate. When these evaporate, they produce a cooling effect on the skin. Major disadvantage of foam formulations is that the propellant technology is relatively complex and expensive to manufacture, thus increasing the overall cost of the final product. The production expense of this type of formulation is most likely the major factor that has limited the number of dermatological foam formulations available to the clinician to date, but this drug delivery offers more patient acceptance [3].

Various physical forces, often occurring concurrently, may contribute to the breakdown of foam once it is dispensed. In simplest terms, these forces involve the variation in air pressure between the air in the bubbles and air in the solution or ambient air (the gradient is higher in smaller bubbles), gravitational forces based on differing densities of the phases, and mechanical breakdown. The type and amount of foaming agent mainly affects density and stability of the foam. Polymers such as xanthan gum and cellulose and can be used to increase foam stability. The specific characteristics of the foam can be modified to establish durability of the foam. The density of foams is approximately one-tenth that of traditional vehicles. Easy spreadability of foams is recognized as a benefit in treatment of large surface areas and hair-bearing skin, but it is also a beneficial for inflamed skin. This is because ease of spreading reduces the need to apply pressure or maintain prolonged contact with the sensitive diseased area. Additional benefits of foams include lack of stickiness or shininess upon application and, conversely, a tendency to absorb and penetrate quickly. Upon application to hair-bearing skin, the foam vehicle breaks down, allowing the super-saturated secondary formulation to travel down the hair shaft and enter the stratum corneum via the appendageal route. Unlike low viscosity solutions, which can flow away from the application site, foams tend to remain in the area where they are applied. Patients have demonstrated a preference for and a high level of acceptance of foam drug delivery [11].

Penetration of drug through skin

Skin structure provides effective protection and barrier to the entry of many compounds in the cells. There are three potential pathways for penetrating molecules into the viable tissue are, through hair follicles with associated sebaceous glands, via sweat ducts, or across continuous stratum corneum between these appendages. This route contributes negligibly to steady state drug flux. This pathway may be important for ions and large polar molecules that struggle to cross intact stratum corneum. Polymers and colloidal particles can target the follicle. The intact stratum corneum layer thus acts as the main barrier. Penetration of many molecules occurs through skin via this intercellular micro route and therefore many enhancing techniques aim to bypass or disrupt elegant molecular structure design. Viable layers may cause metabolization of a drug or activate a prodrug. Deeper dermal regions do not significantly influence absorption while the dermal papillary layer is rich with capillaries hence most of molecule penetrates within short period of time [2].

Structure of skin, physiochemical properties of drug and formulation, manner and frequency of application mainly influence on absorption of drug through skin. Foam drug delivery offers an excellent alternative that can provide the necessary characteristics for delivering the active compounds at high partition but easiness to maintain the application to the targeted areas than liquid dosage form because of low viscosity and high spreadability liquids. Immediately after application of foam on skin surface, the foam lattice breaks down and deposits its active compounds directly on the intended site. These characteristics are particularly advantageous when the foam is used on hairy regions of skin such as to treat scalp seborrheic dermatitis. When the foam is in contact with skin surface, surface interaction changes the film forming system and breaks the film. The gas is released and the residue is deposited on the surface of skin. The gas release is usually accompanied by the loss of volatile entities in the formulation, which result in an increase in absolute concentration of the active molecule in the formulation. The higher concentration will establish a greater concentration gradient; translate into a higher partition rate of the active molecule into the skin surface. In some formulations film stability can be controlled by using thermo-sensitive surface active agents or surfactants. Some surfactants can form a stable foam structure at a low temperature for a long time, increasing the ambient temperature can weaken the film-forming ability and accelerate the collapse of the foam [12].

Influence of Injection Pressure on Foam Quality

Pressure gradient in the sediment is one of the key consideration in the application of foam drug delivery. The concentration of surfactant in the foaming solution influences the injection pressure for foam transport in porous medium. Higher the surfactant concentration, stronger the foam produced, and higher injection pressure. Quality of foam has a significant influence on the foam stability. Therefore, foam quality affects the pressure gradient in foam flow. The foam injection pressure as a function of foam quality has to be studied for an effective foam delivery design [8].
Beside the unique property of foam drug delivery to deliver active compounds, clinicians and patients may find another advantage of using foam in terms of its ease of application. Several studies reported that patient gives higher preference to foam than other dosage form like cream or ointment due to easy application, uniform spreading, less stickiness, less greasy feeling, less dense and therefore generally easier to spread and leave relatively less residue on skin surface. The quick absorption of the foam with less residue is found to be more acceptable because it doesn’t interact with cloths or other material in contact with the applied site. The greasy feeling of many creams and ointments is less reported with foam system, although the hydrating effect especially from emollient foam is comparable. Alcohol contents in foams, as in hydroalcoholic foams may promote fast drying and defatting, which may not be comfortable for consumer with dry skin, but it is found to be useful in oily application sites.

**Evaluation of foam drug delivery system**

Evaluation of foam drug delivery system mainly includes following parameters such as,

- Foam viscosity
- Foam drainage rate
- Foam deformation study
- Foam structure

The volume fraction of liquid in liquid foam is the most important parameter in affecting foam structure. There are different methods to determine foam structures are,

- Electrical Conductivity
- External Pressure
- Macrophotography
- Low-Power Light Microscopy
- Freeze Fracture
- Magnetic Resonance Imaging (MRI)
- Video Microscopy

Video microscopy is a relatively new technique involving the connection of a video camera to a microscope lens using a light pipe. Since the lens can be positioned very closely to the specimen, images are always shadow free [13].

Foams find their applications in pharmacy as aqueous and non-aqueous spray preparations for topical, vaginal and rectal medications and for burn dressings. Because of their high interfacial tension and interfacial area, foams are unstable in the thermodynamic point of view. On the other hand, solid foams are stable, can be prepared from many different materials such as polymers, ceramics, metals and their composites have been studied for their potential use as implants in tissue engineering applications. As illustration, several published patents and articles have described biopolymer or calcium phosphate foams for their tissue repair action and reconstruction containing collagen and calcium phosphate, hydroxyapatite or demineralised bone. Other examples mainly include collagen foams used as haemostatic agents, scaffolds for tissue repair, and supports for cell growth [7].

**CONCLUSION**

Despite the relatively higher costs associated with the development and manufacturing of these formulations, data suggest that foams may not in actual use cost more than other formulation types. Amongst all topical dosage forms and delivery systems, foams have several distinctive properties, which have been proven beneficial to use because of its ease in application, instant absorption and more patient compliance. In future more emphasize should be given for delivering wide categories of drugs in dermatological disorders with foams.

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**REFERENCE**