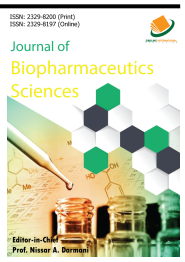
ZIBELINE INTERNATIONAL PUBLISHING

ISSN: 2329-8200 (Print)
ISSN: 2329-8197 (Online)

CODEN : JBSOC4

Journal of Biopharmaceutics Sciences (JBS)

DOI : http://doi.org/10.26480/jbs.01.2017.05.09



CrossMark

DEVELOPMENT OF PHARMACEUTICAL FOAM BASED TOPICAL DRUG DELIVERY SYSTEM

Meghana S. Kamble[1*], Sandhya P. Sutar[1], Saurabh A. Shinde[1], Pravin D. Chaudhari[1], Ashok V. Bhosale[2], Basavaraj K. Nanjwade[3]

[1]Department of Pharmaceutics, P. E. Society's Modern College of Pharmacy, Nigdi, Pune-411044, Maharashtra, India
[2]Department of Pharmaceutics, P. D. E. A.'s S. G. R. S. College of Pharmacy, Saswad, Pune, Maharashtra, India
[3]Department of Pharmaceutics, Faculty of Pharmacy, Omer Al-Mukhtar University, P. O. Box 919, Tobruk, Libya
**Corresponding Author's E-mail: formeghana@yahoo.com*

ARTICLE DETAILS

Article History:

Received 7 January 2017
Accepted 10 February 2017
Available online 15 February 2017

ABSTRACT

Topical drug delivery remains the popular choice of treatment for most of the dermatological diseases. Although the semisolids and liquids remains the choice of dosage forms, there is need of improved drug delivery systems which can be easily applied to areas where application of conventional dosage forms is difficult. Topical foams are novel carriers for such applications and gaining popularity due to their stable, non-toxic, non-irritant nature and ease of application. The foams consist of an emulsion in pressurized container with propellant gas for cosmetic and dermatological uses. The aim of this article is to review the formulation and characterization of foam-based drug delivery.

KEYWORDS

Arbuscular mycorrhizal fungus, root damage, mycorrhizoremediation

1. INTRODUCTION

Topical delivery of drugs is the most commonly used for symptomatic relief, control or cure of dermatological diseases. Based on a study, it is preferred over other routes because of the overall safety and minimum risk of systemic exposure and associated side effects [1]. There are a number of dosage forms available for topical use viz. gels, ointments, creams, liquid formulations.

The vehicles/formulations used for topical delivery significantly influence drug performance. Due to barrier properties of the epidermis, passage of drugs through the stratum corneum is low even with optimized vehicles. This demands development of new and further optimized vehicles for topical delivery of drugs. Foam based drug delivery shows the potential to fulfill most of the requirements of increased permeation/passage of drug through stratum corneum, ease of application and improved aesthetic appearance. According to a study, in the United States Pharmacopeia 32 (General Chapters: 1151), a foam aerosol is defined as an emulsion containing one or more pharmaceutical active ingredients, surfactants and also aqueous or non-aqueous liquids, propellants [2].

Study showed, aerosol foam is normally packed in the container as an emulsion, in which the liquefied gas propellant is dispersed as droplets throughout the aqueous phase; when the emulsion is discharged, the propellant vaporizes into a gas that is trapped by the aqueous solution and this forms foam [3].

Foams are sealed in canisters with pressure in the form of emulsion or suspension or solution. Foam is created at the time of use and exists only for a brief duration. Depends upon ejection the propellant boils and diffuses while the foaming and bodying agents support the development of the crisp, white foam matrix. An emulsion, in the can is converted to a foam and then back to an emulsion as the foam collapses.One should consider pharmaceutical foams as a 'transition state' between the devices for foam generation e.g. aerosol container and the skin of the patient.

2. PREPARATION AND ADVANTAGES

2.1 General Method of Preparation

Step 1: Aqueous Phase, gelling agent and surface active agent are dissolved in water with agitation. The solution is warmed to 50-70 ^{0}C. Water soluble cosmetic or pharmaceutical active ingredients and optional water soluble ingredients are added with agitation to the aqueous phase mixture.

Step 2: The warm hydrophobic phase is gradually poured into the warm aqueous phase with agitation and followed by high speed homogenization. The mixture is allowed to cool to ambient temperature.

Step 3: Hydrophilic Phase the hydrophilic solvent is heated at same temperature. Oil soluble cosmetic or pharmaceutical active ingredients and optional oil soluble formulation ingredients are added with agitation to the hydrophobic phase mixture.

Step 4: The mixture at ambient temperature is added to an aerosol container, the container is sealed and appropriate amount of propellant (about 10 % of the composition mass) is compressed into the container.

In case of heat sensitive active ingredients, add the active ingredients with agitation to the mixture, after step 3.

2.2 Advantages of Foam Based Drug Delivery

1. Foams shows initial higher penetration rate when compared with creams, ointments, lotions, solutions and gels which means higher bioavailability in the earliest possible time post application [4].
2. It easily spreads over large areas and it does not leave a greasy and sticky or oily film on the skin after application [5].
3. It can be applied to limited as well as large areas as per the requirement. It also eliminates the use of mechanical force during application which is known as 'Minimal-touch' therapy [6].
4. Also ease of application to various body cavities like vaginal, ear, rectal etc [7-9].

5. If the medicated foams are sterile, the dose can be removed without contamination of remaining material so this assures maintenance of sterility till last application [10].

6. The medication can be delivered directly to the affected area with improved cosmetic appeal.

7. The medication can be applied in a thin layer.

8. Relative low density contributes to ease of distribution on the scalp or other hairy areas.

9. Quick absorption of the foam with fewer residues is found to be Í ÏÒÅ ÁÃÀÅÐÔÁÂÌÅ ÂÅÃÁÕÓÅ ÉÔ ÄÏÁÓ ÎÏÔ ÍÎÔÅÀÒÁÅÔ ×ÉÔÈ ÀÌÏÔÈÉÎÇ ÏÒ ÏÔÈÅÒ Í ÁÔÅÒÉÀÌ É Î ÄÏÎÔÁÂÔ ×ÉÔÈ ÔËÄ ÁÐÐÌÉÄÄ ÓÉÔÅ8

3. FORMULATION CONSIDERATIONS

One of the important qualities which have a high significance is the so-called foam 'breakability'. According to this property, foams can be classified into several categories having very different application properties.

1. Most of the foams used in pharmacological applications are aerosol foams which come in two or three-phase systems and are 'Quick-breaking' foams.

2. Quick breaking foams after valve actuation breakdown in seconds into a liquid which spreads easily on the applied surface.

3. Quick breaking foams are thermally unstable and collapse upon exposure to skin temperature.

4. Hydro-ethanolic foams are typically thermally unstable and, therefore, their application to large skin areas is cumbersome.

5. Lathers are soapy foams that remain stable as they are formed or increase in volume when rubbed (like shaving foam).

6. Breakable foams are stable at skin temperature, but collapse and spread easily upon application of mild shear forces.

7. The thermal stability of the breakable foams coupled with their fast collapse and high spreading properties make them ideal for use in dermatological and mucosal tissue application.

3.1 Propellant

Research showed material that is liquid under pressurized conditions existing inside the container but that forms gas under normal atmospheric conditions [11]. Propellant is responsible for developing the proper pressure within the container and it expels the product when the valve is opened and aids in atomization during foam production. Propellants are key components of topical foams and make foams unique, as they can be self-generating under the loss of propellants on valve actuation.

According to a researcher, the selection of an 'ideal' propellant is not easy because of the wide variety of available compressed gases, hydrocarbons, chloroflurocarbons (CFCs), hydrchloroflurocarbons (HCFCs), dimethyl ether and hydrofluroalkanes (HFAs) [12]. Nitrogen, nitrous oxide and carbon dioxide are typical compressed gas propellants; they are cheap, but their low boiling point (<-50 0C) may be a concern for consistent accurate dosing since a pressure decrease inside the pressurized foam canister is possible during use. This system is typical for whipped creams and toppings and several pharmaceutical and veterinary products. When this system is used, the gas dissolved in the concentrate will evolve and cause whipping of emulsion into a foam.

N-butane, isobutene and propane are hydrocarbons that are relatively inexpensive and have high boiling point (>42 0C) without the metering problem of compressed gases. However potential safety hazards arise due to their high flammability and explosivity. Therefore, extensive precautions are essential during their manufacture, storage, use and disposal.

Dimethyl-ether has a boiling point of 24.8 0C is another alternative for generating topical foams, but is still flammable. Chloroflurocarbons (CFCs) and hydrochloroflurocarbons (HCFCs) do not have the problem of flammability, because of their high boiling points compared to hydrocarbons and have widely been employed as pharmaceutical propellants. These types of propellants have an ozone layer depletion effect and thus, there are legislative restrictions on their use. Thus during the past decade HFA propellants such as difluroethane (HFA 134a) and heptafluropropane (HFA 227) have been gaining more attention for pharmaceutical use. HFAs are ideal for topical foam generation since they have a high vapor pressure (572 and 390 kPa for HFA 134a and HFA 227, respectively). Furthermore, HFAs are non-explosive, non-flammable and non-chlorinated, with no concerns regarding ozone depletion [13].

3.2 Foaming Agents

These are generally surface active agents (surfactants), also in some cases proteins and particles are used as foaming agents. Surfactant's HLB value is important while selecting an ideal agent. The choice of surfactant also depends on the type of emulsion desired. When the emulsion is of oil-in-water type it requires an emulsifier of HLB value of 9-14. Study showed if foam is of water-in-oil type, it requires emulsifier with an HLB value of 4-9 [14]. Pharmaceutical formulations use both ionic as well as non- ionic surfactants. But ionic surfactant causes skin and mucosal irritation so non-ionic surfactants are preferred, particularly when the target area of treatment is infected or inflamed.

On valve actuation and the rapid evaporation of propellants, the foaming agents can get adsorbed at the air- water interface or other solvent in order to reduce interfacial tension.

3.3 Solvents or Co-solvents

Solvents used are of two types: aqueous and non- aqueous. In most cases topical foams are water-based since the generation of non-aqueous foams is more difficult. Emollient foams which are used for cosmetic purpose consists of oil components, which can be selected from all pharmaceutically acceptable oils, including mineral oils and capric/ caprylic triglycerides, fatty acid esters (e.g. isopropyl myristate, isopropyl palmitate and isopropylisostearate, isopropyl adipate) and essential oils. In some cases the oil may be selected for its therapeutic benefit e.g. as a protective agent.

3.4 Viscosity Modifying Agents

It is also called as gelling agent. It is used to facilitate the creation of foam with desirable texture and optimum spreading properties. Concentration of gelling agents is in the range of approximately 0.05- 2.0% w/w. There are many types of gelling agents from natural (e.g. xanthum gum), semi-synthetic (e.g. cellulose ethers) or synthetic origin (e.g. polyvinylpyrrolidone).

Sometimes mixtures of above can be used to improve foam properties. Also some of the gelling agents also possess a film-forming property which helps to form uniform layer of active ingredient on the skin.

3.5 Other Excipients

Other excipients like antioxidants, acids can be used to enhance drug solubility and/or to maintain the pH of the formulation in a favorable range to enable the maximum amount of drug to be formulated. Topical foam can contain a cooling agent (e.g. menthol), a warming agent (e.g. polyhydric alcohols) or a soothing agent (e.g. aloe vera) to generate a unique sensation or sensation modifying effect on application of the foam.

4. CHARECTERIZATION OF FOAMS

The European Pharmacopoeia describes two characterization methods in the Monograph "Medicated foams". These are firstly estimation of the relative foam density as an indication of the foam firmness and secondly, the foam expansion time as a parameter of the formability of the formulation. Density of produced foams is determined by weighing a predefined volume of foam compared to the weight of the same volume of water (Equation (1)).

$$FD = \frac{m\,(foam)}{m\,(water)} \qquad (1)$$

with m (foam) is mass of foam per volume unit (g); m (water) is mass of water per volume unit (g).

For determination of foam expansion time, foam volume is released into a burette and the resulting foam expansion is assessed within a defined time.

The foam in this case is produced in a vertical cylindrical vessel provided with a small indentation in the centre of its base. The rounded end of a glass rod is placed in this indentation and the rod is held vertically by an upper support. Withdrawal of the support allows the rod to fall against a wall of the vessel. The time of fall is used empirically as a measure of foam consistency. Further methods to measure foam consistency such as determinations with mobilometer, foam consistometer and Brookfield viscometer.

4.2 MicroscopicEvaluation

Foams can be characterized macroscopically with the determination of characteristics such as being fine pored or coarsely porous, viscous or runny.

4.3 Foam Bubble Size/Microscopic Evaluation

Bubble size and structure of generated foams can be observed and measured with a stereo microscope connected with a digital ocular. Foam uniformity can also be determined with this method as homogeneity of air bubbles. The major disadvantage of this method is however that the resolution of these observations is severely limited by the wavelength of visible part of the spectrum. Because of the large semi-aperture angle, they have a small depth of field which reduces the potential for stereo observations of the highly three-dimensional foamed materials. Produced foams can also be analyzed by means of an Image Analysis System (e.g. Sympatec GmbH, Germany). The size (Ferret diameter), roundness and the aspect ratio of incorporated air bubbles as well as bubble amount in a predefined area are parameters of interest in foam characterization. Measurements can be carried out direct after foam generation and after defined time intervals to follow foam destabilization mechanisms which allows for a foam stability assessment.

4.4 Foam Texture

The properties which principally influence foam firmness are surface viscosity, bulk liquid viscosity, bubble size distribution and foam geometry. Foams can be characterized using a Texture Analyzer (TA). The foam should be dispensed into a container and the sample is then stressed with a disk which is pressed through the foam to a specified depth. The required force is recorded. During penetration the force is shown to gradually increase until the point of maximum penetration depth. The sample then proceeds to be withdrawn from the disk. The maximum positive peak indicates the firmness of the foam.

4.5 Determination of Foamability and Foam Stability

This test can be carried out to determine the following parameters: foam expansion (FE, %, Equation (2)), foam liquid stability (FLS, %, Equation (3)), foam volume stability (FVS, %, Equation (4)) and foam gas fraction (GF, ml, Equation (5)).

The foam is discharged into a glass cylinder. Initial volume of foam, the volume of aged foam and the volume of drained liquid after defined time intervals are recorded. By this, the separation of the liquid due to liquid drainage can be observed at 30 min to describe the foam stability over this time period.

$$FE=\frac{V\,(\text{foam})\,-\,V\,(\text{formulation})}{V\,(\text{formulation})}\times 100\% \qquad (2)$$

V (foam), volume of produced foam (mL), V (formulation), volume of formulation to produce V (foam) (mL).

The higher the FE the more foamable is the formulation.

$$FLS(\%)=\frac{V\,(\text{liquid 30 min})}{V\,(\text{formulation})}\times 100\% \qquad (3)$$

V (liquid 30 min), volume of liquid drained after 30 min.

The lower the FLS the more stable is the produced foam.

$$FVS(\%)=\frac{V\,(\text{liquid 30 min})}{V\,(\text{foam})}\times 100\% \qquad (4)$$

V (foam 30 min), volume of foam after 30 min.

The higher the FVS the more stable is the produced foam.

Foam gas fraction can be determined as a difference between foam volume and volume of the expanded formulation.

$$GF\,(\text{mL})=V\,(\text{foam})-V\,(\text{formulation}) \qquad (5)$$

4.6 Foam Stability by Turbiscan Methods

Tyndall light scattering can be used to measure foam stability. This method is based on the Faraday-Tyndall effect which postulates that colloidal solutions can scatter light. The method is based on differences in refractive indices between solution of foaming agent and air resulting in different intensities of transmission and back-scattering. Intensities of transmitted and back-scattered light are dependent on the amount of air in foam. During the process of foam destabilization, the amount of air changes in different depths of the measuring cell as a result of air bubble growth (foam ripening) and liquid drainage. Therefore, transmission and back scattering signals also change. The different refractive indices of both these phases lead to an interaction of photons (diffusion and diffraction). The back-scattering signal is inversely proportional to the square root of the mean free distance covered by a photon being back-scattered (Equation (6)).

$$BS \approx \frac{1}{\sqrt{1^*}} \qquad (6)$$

l*, mean free distance of a photon (m).

The higher the phase volume of gas in foam, the shorter is the free distance covered by a photon and therefore the more intense is backscattering and the less intensive is transmission.

4.7 Rheological Properties

Rheological properties of foams are very difficult to measure, especially for weak foams. Firstly, foams are unstable because of liquid drainage and Ostwald ripening. Additionally, the generation of a liquid film slip layer at the wall during the measurement will affect its accuracy. However, rheological methods may be used in oscillatory mode to learn about foam film elasticity and therefore, foam stability.

4.8 Identification of Propellant

Gas chromatography and infrared spectrophotometer have been used to identify the propellants and also to indicate the proportion of each component in a blend [15].

4.9 Moisture

The Karl Fischer method has been accepted to a great extent to determine the moisture content. Gas chromatography has also been employed for the same.

4.10 Leakage

The leakage of aerosols is carried out by passing the containers through the water tanks. The leakage can be detected by determining change in the temperature of water.

4.11 Net Content

Used to determine whether sufficient product has been filled into each container. The tarred cans that have been placed onto the filling line are reweighed and the difference in weight is equal to the net contents. The other method is destructive method and consists of weighing a full container and then dispensing the contents. The contents are then weighed with provision being made to determine the amount retained in the container.

4.12 Flame Projection

This test indicates the effect of an aerosol formulation on the extension of an open flame. The foam forming product is sprayed for about 4 seconds into a flame. Depending on the nature of the finished formulation the flame is extended the exact length being measured with a ruler.

4.13 Flash Point Determination

This is determined by use of the standard Tag open Cup Apparatus and the aerosol product is chilled to a temperature around 25 0F and transferred to the test apparatus. Finally the test liquid is allowed to increase slowly in temperature and the temperature at which the vapors ignite is taken as the flash point. Although the test is still used the results are of limited value because the flash point obtained is usually the flash point of the most flammable component which in the case of topical pharmaceuticals is the hydrocarbon propellant [16].

4.14 Aerosol Valve Discharge Rate

This is determined by taking an aerosol product of known weight and discharging the contents for a given period of time using standard apparatus. Reweighing the container after the time limit has expired the change in weight per time dispensed is the discharge rate which can then be expressed as grams per second [17].

Table 1: Commercially available foam formulations

Active compounds	Manufacturers	Indications
Betamethasone valerate	Stiefel; Mipharm	Anti-inflammatory and antipruritus
Clindamycin phosphate	Stiefel	Treatment of acne
Clobetasol propionate	Stiefel	Anti-inflammatory and antipruritus
Felbinac	Lederle	Anti-inflammatory
Hexachlorophene	Calgon Vestal	Surgical scrub and bacteriostatic skin cleanser
Hydrocortisone and Pramoxine	Schwartz Pharma; Reed and Carnrick	Anti-inflammatory and anti-pruritus
Permethrin	Foamix	Treatment of lice
Phenothrin	Sutton Healthcare	Treatment of lice
Povidone iodine	Purdue Frederick ; Redi-Products	Relief of scaling and itching due to dandruff
Pyrethrins and piperonilbutoxide	Mipharm	Treatment of lice
Zinc Pyrithione	Quiver Pharmaceutical	Relief of scaling and itching due to dandruff

5. CONCLUSION

Topical route of administration remains popular due to ease of administration and restricted local effect with minimum systemic side effects when needed. Though creams, ointments, gels, solutions and suspensions remain as a preferred choice of dosage form there is a need of improved topical delivery to facilitate application to certain body cavities and scalp. Foam drug delivery systems area a promising option for treatment of many dermatological diseases and may be a suitable solution to the problems associated with topical delivery systems. They have good cosmetic acceptability, chemical stability, homogeneity, nontoxic nonirritant properties. These properties make foams useful to topical delivery vehicles. Although they are very popular in cosmetics the foams are not very popular in the therapeutic/pharmaceutical domain owing to their high costs and comparatively complex preparation methods. However the foam products are now growing in number in pharmaceutical market attracting researchers due to potential ability of pharmaceutical foams to enhance topical drug delivery and bioavailability.

Table 2: Foam formulations under development

Active compounds	Manufacturers	Indications
MupiFoam™	Mupirocin (Bactroban)	Impetigo Infections caused by St. aureus and-hemolytic Streptococci
BetMetFoam™ Emollient	Betamethasone valerate 0.12%	Psoriasis Atopic dermatitis
BetMetFoam™ Oily	Betamethasone valerate 0.12%	Psoriasis Atopic dermatitis
TerbiFoam™ Emollient	Terbinafine 2.0%	Dermal mycoses Dermatophite infections
TerbiFoam™ Watterless	Terbinafine 2.0%	Dermal mycoses Dermatophite infections
AcycloFoam™	Acyclovir 5.0%	Genital herpes Labial herpes
DicloFoam™	Diclofenac 1.0%	Osteoarthritis joints pain Back pain
DicloFoam™	Diclofenac 3.0%	Actinic keratosis
PerFoam™	Permethrin 1.0%	Head lice, Public lice, Scabies.
DEETFoam™	Diethyl toluamide 25.0%	Protection fro m insect bite
LactiFoam™	Ammonium lactate 12.0%	Dry, scaly skin Ichtyosis vulgaris
UreaFoam™	Urea 10%, 20% and 40%	Dry, scaly skin Ichtyosis vulgaris
AtopiFoam™	Non-steroidal agent	Topical dermatitis
BabyFoamixZinc™	Zinc oxide	Diaper rush
Foot Foam™	--	Dry, scaly skin of the foot

ACKNOWLEDGMENT

Authors would like to thank Modern College of Pharmacy, Pune, for providing library facility.

REFERENCES

[1] Leon, H.K., Joseph, B.B. 2012. Topical Foam Formulations, Supplement to Practical Dermatology. Vehicle Matters, 1: 1-21.

[2] Brown, W. 2009. United States Pharmacopoeia 32. General Chapters: 1151, 33 (5): 1260.

[3] Yanjun, Z., Stuart, A., Jones, Marc, B.B. 2010. Review on Dynamic foams in topical drug delivery. Journal of Pharmacy and Pharmacology, 62 (6): 678-684.

[4] Hanafi, T., Xinfan, H., Howard, I.M. 2007. Foams for Enhanced Topical Delivery: An overview. DermatololSinica, 25: 10-15.

[5] Tamarkin, D., Eini, M., Friedman, D. 2006. Cosmetics and Toiletries. Foam: The Future of Effective Cosmeceuticals, Cosmetics and Toiletries Science Applied. 1, http://www.cosmeticsandtoiletries.com/ formulating/function/deliver y/4539471.html

[6] Carryn, H.P., John, M.H., Christian, S., Eric, W.S. 2003. Foam Drug Delivery in Dermatology beyond the Scalp. American Journal of Advanced Drug Delivery, 1 (1): 71-75.

[7] Rodrigo, Y. 2008. www.OticPharma.com.

[8] Arzhavitina, A., Steckel, H. 2010. Review on Foams for pharmaceutical and cosmetic application. International Journal of Pharmaceutics, 394: 1–17.

[9] Loyd V, A., Nicholas G.P., Howard, C.A. 2014. Pharmaceutical Dosage forms and drug delivery system, Ninth Edition, Wolters Kluwer Health.

[10] European pharmacopoeia 5.0. 2005. Foams, Medicated, 604p. http://lib.njutcm.edu.cn/yaodian/ep/EP5.0/07_monographs_on_dosage_forms/Foams,%20medicated.pdf

[11] Patrick, J.S. 2010. Martin's Physical Pharmacy and Pharmaceutical Sciences, Lippincott, William's and Wilkins, 31.

[12] Remington, B. 2005. Remington: The science and practice of Pharmacy, 21 st Edition, Lippincott Williams and Wilkins, Indian Edition, 1004

[13] Swarbrick, J., Boylan, J.C. 2010. Encyclopedia of Pharmaceutical Technology, 1, (2): 758.

[14] Carter, S.J., Cooper, Gunn's. 2008. Dispensing for Pharmaceutical Students, 12th Edition, CBS Publisher, New Delhi, 121.

[15] Leon, L., Herbert, A.L., Joseph, L.K. 1987. The Theory and Practice of Industrial Pharmacy, Third edition, Varghese Publisher, Mumbai, 615.

[16] Swarbrick, J., Boylan, J.C. 2006. Encyclopedia of Pharmaceutical Technology, Second Edition 2, 2648.

[17] Gilbert, S.B., and Christopher, T.R. 2002. Modern Pharmaceutics, Drugs and Pharmaceutical Sciences, Third Edition, Marcel Dekker, Inc, New York-Basel, 72, 566.