

Topical Sprays: Novel Drug Delivery System

Prakarsha Chavan, Amrita Bajaj and Akkshata Parab*

Department of Pharmaceutics, SVKM's Dr. Bhanuben Nanavati College of Pharmacy,
Vile Parle (West), Mumbai - 400 056, Maharashtra, India.

ABSTRACT

Topical drug delivery systems have been found to have many advantages over oral drug delivery systems such as avoidance of first pass metabolism, gastro intestinal irritability, slow onset of action, etc. The clinical evidence indicates that conventional topical formulations possess certain short comings like irritancy, allergies due to the variety of excipients used. This review deals with all detailed information regarding rational approach to novel topical formulations like topical/ transdermal sprays and their formulation, fabrication and evaluation parameters.

Keywords: Topical sprays, Metered dose transdermal spray, Advanced Preservative Free Container.

INTRODUCTION

Over the last few decades the treatment of illness has been accomplished by administering drugs to human body via various other routes in addition to traditional oral and sublingual routes like rectal, parenteral, topical, inhalation, etc. With the advent of new era of pharmaceutical dosage forms, topical drug delivery systems have established themselves as integral part of novel drug delivery products. Topical drug delivery systems (TDDS) are gaining increase in popularity and several drugs have been successfully delivered by topical/transdermal route for both local and systemic action. Topical/transdermal drug delivery systems offer the non-invasive delivery of medication from the surface of skin, the largest and most accessible organ of human body-through its layers, to the circulatory system¹. Topical delivery is the application of a drug containing formulation to the skin to directly treat cutaneous disorders or other effects within the skin. Topical drug delivery systems offer many advantages over conventional injection and oral methods. It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliance and minimizes harmful side effects of a drug caused due to temporary overdose².

The development of TDDS is multidisciplinary activity that encompasses fundamental feasibility studies starting from the selection of drug molecule to the demonstration of sufficient drug flux in an *ex vivo* and *in vivo* model

followed by fabrication of a drug delivery system that meets all the stringent needs that are specific to the drug molecule (physicochemical and stability factors), the patient (comfort and cosmetic appeal), the manufacturer (scale up and manufacturability) and most important the economy. Topical preparations are used for the localized effects at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membranes³.

Advantages of Topical Drug Delivery Systems⁴

- Avoidance of first pass metabolism.
- Convenient and easy to apply.
- Achievement of efficacy with lower total daily dosage of drug due to continuous drug input.
- Avoidance of gastro-intestinal incompatibility.
- Improve patient compliance.

Limitations of Topical Drug Delivery Systems⁵

- Skin irritation and contact dermatitis may occur due to the drug and/or excipients.
- Can be used only for drugs which require very small plasma concentration for action.
- Drugs of larger molecular size are not easy to be absorbed by the skin.

Topical dosage forms, an alternative to conventional formulations, are becoming popular because of their unique advantages. The topical

drug delivery systems are mainly used in pain management, contraception, infections, allergies, inflammation and urinary incontinence.

Various novel topical dosage forms include:

- Topical gels
- Topical sprays
- Topical patches
- Topical films

Topical gels

Gels are transparent to opaque semisolids containing a high ratio of solvent to gelling agent. Gels are created by entrapment of large amounts of aqueous or hydroalcoholic liquid in a network of colloidal solid particles, consisting of inorganic substances, such as aluminum salts or organic polymers of natural or synthetic origin. Depending upon the nature of colloidal substance and the liquid in the formulation, the gels range in appearance from entirely clear to opaque. Most topical gels are prepared with organic polymers, such as carbomers, that impart an aesthetically pleasing, clear, sparkling appearance to the product, and are easily washed off the skin with water⁶.

Topical patches

A topical patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. The first commercially available topical prescription patch was approved by the U.S. Food and Drug Administration in December 1979, namely scopolamine patch for motion sickness⁷. The adhesive is covered by a release liner, which needs to be peeled off before applying the patch on the skin.

Topical films

These are medicated transparent polymeric films similar to topical patches. The only difference is that films do not contain adhesive polymer.

Topical sprays

Topical sprays are dosage forms in which polymeric solution of drug is sprayed over the intact skin so as to get a sustained release of drug from the polymeric matrix. The drug is present in saturated form in the polymer matrix. As the organic solvent vehicle evaporates, slowly the drug diffuses through the polymer matrix and passes from the skin barrier.

Introduction to Topical sprays

The history of aerosol technology is traced back to the early years of the twentieth century. The principles of aerosol technology were applied to the pharmaceutical aerosols in early 1950s. The topical aerosol products were intended for application for treatment of burns, minor cuts, bruises, infection and various dermatological conditions. Historically, developments in topical drug delivery have been incremental, focusing on overcoming problems associated with the barrier properties of the skin, reducing skin irritation rates and improving the aesthetics associated with conventional topical drug delivery systems. Regardless of the transdermal/topical drug delivery systems in development, the patient acceptability from an aesthetic, safety and non-irritancy perspective will remain the main focus for the newer products entering the market. The non-invasive character of transdermal drug delivery makes it accessible to a wide range of patient population and is a highly acceptable option for drug dosing.

Problems with existing technology

Transdermal/topical drug delivery systems (TDDS) such as patches, creams and gels still suffer from some limitations⁸. The precision of dosing is particularly an issue with creams and gels, especially as it has also been demonstrated that altering the dose applied per surface area can affect the drug delivery profile, although conflicting effects have been observed when the area of application is increased⁹. Although precision of dosing might be less of an issue in patch systems, there is relatively little flexibility available for the dosing. Variability of dosing has also been highlighted as an issue with TDD systems. Most studies have focused on the intra-site variability¹⁰ of dosing that many have attributed to the different levels of skin hydration found at various anatomical sites. It has also been shown that variations in temperature, possibly due to local microcirculation changes in the skin, can affect the drug delivery profile from TDDS. Variability of dosing has also been observed between different skin types, skin of different aged patients¹¹ and diseased skin¹².

Psychological stress has also been shown to impact skin barrier recovery. The relatively high skin irritation rates that were associated with the earlier transdermal patches have been somewhat reduced, but the inherent occlusive nature of the products still dictates that this

remains an issue for TDDS¹³. The occurrence of sensitization reported has been up to 50% with clonidine patch and seen to increase with time of exposure¹⁴. As consumers become increasingly educated about product options, their expectations regarding skin irritation rates and patch size have also been increased. From the patient's perspective, the large surface area for application, particularly for gels and creams, which is required to produce adequate dosing levels, can also translate into aesthetic concerns. It is crucial that formulators consider the aesthetics of the product after application, to avoid unpleasant stickiness or greasiness and to minimize residue on the skin. A recent development that attempts to overcome some of the limitations of TDDS involves application of the concept of evaporative delivery and formulating aerosol.

The concept of evaporative delivery- topical aerosol sprays

Traditionally, aerosols as topical spray systems were largely used as a medium for transdermal drug delivery. Aerosols are those products that depend on the power of a compressed or liquefied gas to expel the content from the container. However, these propellants based sprays have now been replaced by propellant free and polymer based Metered dose transdermal sprays (MDTS).

The MDTS is a topical solution made up of a volatile and nonvolatile vehicle containing the drug dissolved as a single-phase solution. A finite metered-dose of the formulation applied to intact skin results in subsequent evaporation of the volatile component of the vehicle, leaving the remaining nonvolatile penetration enhancer and drug to rapidly partition into the stratum corneum during the first minute after application, resulting in a stratum corneum reservoir of drug and enhancer. It is diagrammatically represented in Figure 1. Following a once-daily application of the MDTS a sustained and enhanced penetration of the drug across the skin can be achieved from the stratum corneum reservoir. Increases in drug diffusivity are related primarily to stratum corneum lipid fluidization or lipid phase separation¹⁵.

This formulation represents a micro-dose evaporative system that provides passive and non-occlusive delivery. The system developed is a rapid-drying solution containing a volatile component that enables the volume per area of application to be precisely defined. This

component also enables the formulation to have uniform distribution on the skin over a defined area after application, without leaving excess vehicle. Hence, this ensures that the dose can be administered in a precise and highly reproducible manner and that aesthetic value and transference issues are avoided. The evaporation of some of the vehicle leads to an increase in concentration of the active drug and hence enhanced partitioning into the stratum corneum.

The non-volatile component prevents the drug from precipitating from solution as the volatile solvent component evaporates. The physicochemical properties of the nonvolatile component have been selected so that it partitions rapidly into the stratum corneum and serves to disrupt the ordered intercellular lipids and enhance permeation. Hence, this type of delivery system creates an invisible depot of drug and enhancer in the stratum corneum from which the drug can be slowly diffused into the skin. MDTS relies on the combination of newly identified GRAS (Generally recognized as safe) chemical penetration enhancers and the accurate and precise topical dosing of volatile and non volatile vehicles¹⁶.

The MDTS has the potential to offer enhanced passive topical drug delivery system with little or no skin irritation primarily as a result of its non-occlusive nature and the skin tolerability. Improved cosmetic acceptability compared to patches, gels, and creams has been achieved through the judicious use of excipients. The product is more convenient to use, since it is into compact unit and can be applied easily and quickly. The MDTS features a small, discrete, hand-held applicator that delivers a pre-set dose of a proprietary formulation of drug to the skin and the package is tamper proof system. It also prevents contamination of unused contents. The inherent dosage flexibility of the MDTS and the simplicity of manufacture provide a significant cost-of-goods advantage relative to traditional transdermal systems.

This delivery system allows for patient friendly, discreet and convenient, dosing via topical administration, thus avoiding gastro-intestinal tract irritation. It provides many advantages over patches and gels, including a non-messy application with little or no skin irritation. Metered-dose transdermal spray has the potential to expand the growth of TDDS by broadening patient acceptance and pharmaceutical applications for enhanced TDD.

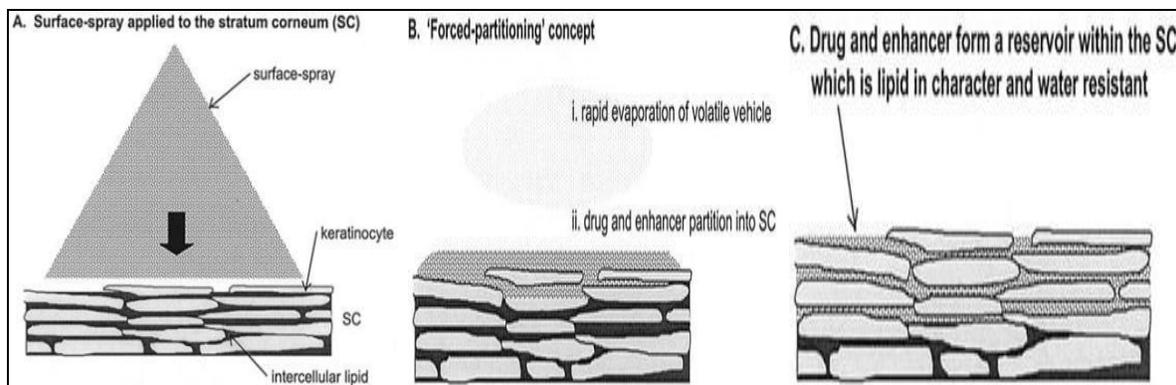


Fig. 1: Schematic representation of the partitioning process for a rapid-drying, topical spray formulation

Advantages of the Metered Dose Transdermal Spray Formulations

- The product is more convenient to use, since it is into compact unit and can be applied easily and quickly.
- It has potential to offer enhanced passive topical drug delivery with little or no skin irritation primarily as a result of its non-occlusive nature and the skin tolerability.
- Improved cosmetic acceptability compared to patches, gels and creams has been achieved through the judicious use of excipients.
- This technology can be used to evaluate the feasibility of topical delivery for newly developed drugs.

Metering pumps are used now a day to provide propellant free delivery.¹⁷ Pump technology has made enormous advances as a result of the fluorocarbon ban in 1976.

When finger is pressed on the actuator, the piston and clapper descend. The dose chamber gets closed and further finger pressure causes an increase in hydraulic pressure in the liquid isolated in the dose chamber. As the liquid cannot be compressed it counters the action of the spring and pushes back the clapper towards the base, passes through the centre of the stem and gets atomized by the spray insert.

Metered Dose Topical Spray Package Components

Metered Dose Topical Spray aerosol product comprises of four separate components.

A. Product concentrate

B. Propellant

C. Container

D. Valve/ Metering pumps and actuator

Last two components are collectively called as packaging component.

A. Product Concentrate

Product concentrate consists of a single or combination of active ingredients and contains other ingredients depending upon the type of MDTs formulation. The product concentrate comprises of the following:

1. Active Ingredient

The topical/transdermal route is an extremely attractive option for the drugs with appropriate pharmacology and physical chemistry. The foremost requirement of MDTs is that the drug possesses the right mix of physicochemical and biological properties for topical/transdermal drug delivery. Active ingredient used for metered dose topical spray must be therapeutically effective at a relative low dose and have a lower molecular weight, be non irritating to the skin surface and should have some affinity for the skin, it should dissolve in the fatty matrix between the skin cell. It should be stable and compatible with the vehicle or solvents used in the formulation.

The MDTs is specially used in chronic pain management, central nervous system disorders including nausea, anxiety-related conditions and Alzheimer's and Parkinson disease, menopause, female androgen insufficiency, male androgen insufficiency, contraception, urinary incontinence, smoking cessation¹⁸. Some of the drugs incorporated in sprays include Estradiol, Nestorone, Fentanyl, Nicotine, Buspirone, Granisetron, Testosterone, Hydrocortisone aceponate.

2. Solvents and Co-solvents

Volatile solvents: It is most desirable that, after application of the drug composition to the skin, the volatile component of the composition evaporates and the area of skin to which the drug composition was applied becomes touch-dry.

Nonvolatile vehicle: Normally non volatile solvents are selected based on the miscibility with volatile solvents. The selection is also based upon the polymer solubility in solvent. The solvent helps to spread the drug and the penetration enhancer over the skin. For example methanol, ethanol, acetone, isopropanol, ethyl acetate, methylene chloride has been used as solvent.

Co-Solvents perform a variety of functions in topical aerosol formulations. While selecting co-solvents various factors like stability, safety, compatibility must be considered. Co-Solvents help to reduce vapour pressure of propellant. Co-Solvents also help in solubilizing the drug in the system¹⁹.

3. Film forming Polymers

These macromolecules are very large molecules consisting of many repeating units and are formed by a process of polymerization which links together small molecules, monomers. For example: Carbomer or carbopol, Poloxamer (or pluronic), Polymethacrylates (Eudragits) etc. Such film forming polymers are utilized in the development of Metered dose transdermal sprays. Diffusion of the drug through the polymer and absorption through the skin barrier are the rate limiting steps.

They are dissolved in to the non-volatile solvent along with permeation enhancer and the drug is dissolved in volatile solvent. After evaporation of solvent they form film onto the skin surface which releases the drug and this drug goes to systemic circulation to give effect. Following factors are taken into consideration during the selection of polymer:

1. Molecular weight and chemical functionality of polymer must allow proper diffusion and release of specific drugs. Increased polymer weight decreases drug diffusivity in polymers.
2. Polymer should not react with the drug.
3. The polymer and its degradation products must be non-toxic.
4. The polymer should not decompose on storage or during the useful life of device.

5. The polymer must be easy to manufacture and it should yield itself into desired product and should allow incorporation of large quantities of active component without deteriorating its mechanical properties.
6. 6. Cost of polymers should not be excessive.

Different polymers used are:

Various grades of Eudragits (Eudragit type RSPO, L-100, RL-100, RLPO, S-100), polyvinyl acetate, cellulose acetate, poly vinyl alcohol, povidone vinyl acetate, polyvinylpyrrolidone (Kollidon K-30, Kollidon K-25 and Kollidon VA 64), cellulose derivatives such as Ethyl cellulose, Hydroxy ethyl cellulose, Cellulose acetate phthalate, Hydroxy propyl methyl cellulose type K4M and K15M, Carbomers, Poloxamer etc²⁰.

4. Penetration enhancers

A dermal penetration enhancer is an agent that facilitates the passage of an active agent through the skin. The dermal penetration enhancing compounds are of low toxicity to the skin and thus are safe at high concentration, are non-irritating, and excellent promoters of percutaneous absorption. These are compounds, which promote skin permeability by altering the skin as a barrier to the flux of a desired penetrant. Mainly used penetration enhancers are terpenes, terpenoids or essential oils, pyrrolidones and azones, fatty acids and esters, alcohols, glycols, glycerides, surfactants and phospholipids²³.

5. Solubilizers

The solubilizers are used to dissolve or suspend the drug in chosen vehicle. Solubility influences a drug's dissolution, release kinetics, and ultimately its bioavailability and thus plays a major role in the formulation of drug delivery systems. Many of the solubilizers also enhance percutaneous penetration of the drug and/or act as humectants. Preferred solubilizers include surfactants such as SLS (Sodium lauryl sulphate), polyhydric alcohols like propylene glycol or polyethylene glycols, vitamin E TGPS (tocopheryl polyethylene glycol 100 succinate) and labrasol etc.

6. Plasticizers

Plasticizers are additives that increase the plasticity or fluidity of a material. Plasticizers work by embedding themselves between the

chains of polymers, spacing them apart (increasing the "free volume"), and thus significantly lowering the glass transition temperature for the polymer and making it softer. Plasticizer includes triethyl citrate, dimethyl isosorbide, castor oil, polyhydric alcohols such as propylene glycol or polyethylene glycol.

7. Humectants

In the presence of water the permeability of skin increases significantly. Hydration is the most important factor which increases the permeation capacity of skin. Hence, humectants are used in the formulation of topical/transdermal formulations. Humectants used includes polyhydric alcohols e.g. propylene glycol, polyethylene glycol, glycerol, sorbitol, butylene glycol and polyvinylpyrrolidone^{21, 22}.

B. Propellants

The propellant is the "Heart" of the aerosol product. The propellant is defined as "liquefied gas with a vapour pressure greater than atmospheric pressure at a temperature of 105° F". For the topical aerosols, the propellant is one of the essential but now optional components of the entire package. It performs dual functions: supplies the necessary pressure to expel material from the container when the valve is opened and helps to convert the product into the desired physical form for its end use. Propellant is necessary for developing proper pressure within an aerosol container and for expulsion of the composition when the valve is open. It is also responsible, together with the valve, for dispensing the product as a fine spray.

C. Packaging Components

MDTS has three packaging components:

1. Container
2. Metering valve/ pump
3. Actuator

1. Containers

Various containers have been used for pharmaceutical aerosols. Because of esthetics and excellent compatibility with drugs, glass, stainless steel and aluminium containers are selected. MDTS formulation makes use of plastic coated glass bottles ranging in size from 10ml to 30ml for solution aerosols. Clarity of the content can be checked in the path of strong light using glass containers. All commercially available glass bottles have 20 mm neck finish and adapt easily to all of the metered aerosol

valves presently available. Specially designed glass bottles having „V" shape carved at the base are used. The dip tube of the pump fits in this 'V' shape cavity such that the last drop of the spray can also be sprayed out. There are also customized containers available from various manufacturers²⁴.

2. Metering Valves/ Pump

Aerosol valves are used for dispensing aerosol products as sprays, foams and semisolid streams. The MDTS technology utilizes metered dose valves for delivering definite amount of drug per actuation or per spray. Metered valves have been developed to dispense given quantities of medication, thus metering and controlling the dose delivered. The use of metering pumps helps to deliver propellant free delivery as external pressure is required to actuate the content present inside the container. The metered aerosol pump ensures accurate dosing onto the intact skin and eliminates many of the administration problems. Pumps are designed to accurately deliver volumes as low as 25µl and as high as 0.5 to 1 ml per actuation. Two types of pumps namely VP7 and VP3 are available in markets which are made up of pharmaceutically acceptable materials such as polypropylene and polyethylene. A special range of VP7 pumps such as VP7H (as in Figure 2) which is resistant to hydrocarbons has also been developed by Aptar Pharma²⁸. Functions of the metering valves are to meter accurately and repetitively small volumes of liquid containing the drug and to seal the pack against undue leakage of propellant vapour and to deliver product in the desired form.



Fig. 2: Vertical Action Valve

Pumps have two main functions

A. Dynamic Function

Delivers metered dose of liquid or viscous pharmaceutical formulation. Spray (liquid) or

dispense (viscous product) with ergonomically designed actuators. In some instances, pumps also participate in the product protection (oxidation/contamination).

B. Static Function

Closure: Sealing of the container and protection of the content at rest

Compatibility: No absorption/ adsorption, low level of extractables or leachables from components of the pump.

3. Actuators

Precision molded plastics constructed from a variety of polyethylene or polypropylene materials by injection molding. Accurate dimensional control is required for critical areas like spray orifice to ensure absence of leakage and correct spray performance during discharge. Topical spray actuators of different shapes and sizes are available²⁵. Actuator incorporates the discharge orifice or spray nozzle and a socket to engage and form a seal with the metering valve system. In case of metered dose topical spray formulations, a centrifugal type spray nozzle (as in Figure 3) controls the spray angle (α) and nozzle shroud controls the height (h) of the spray nozzle above the skin. The nozzle shroud also ensures the nozzle orifice is kept perpendicular to the surface of the skin. By controlling the parameters like concentration of drug and enhancer in the vehicle, the spray volume, angle and height, the formulator can control the total application area of the spray

and concentration of drug/enhancer per unit area of skin.



Fig. 3: Representative Picture of Actuator

Selection of Container

APF Plus (Advance preservative free) screw-on spray container from Aptar pharma (as seen in figure 4) was procured for delivering the accurate amount of drug from container. Spring loaded tip seal mechanism acts as a physical barrier avoiding crystallization and contamination of the product, clogging of nozzles can be avoided. Micro filter membrane in the air flow prevents the product from contamination. The APF Plus spray system ensures accurate dosing and elimination of many of the administration problems. The concept of propellant and preservative free metered delivery offers a new dimension to deliver potent therapeutic agents.

APF PLUS Advantages

- Fine mist
- Round spray pattern
- Long and stable fully developed phase of spray

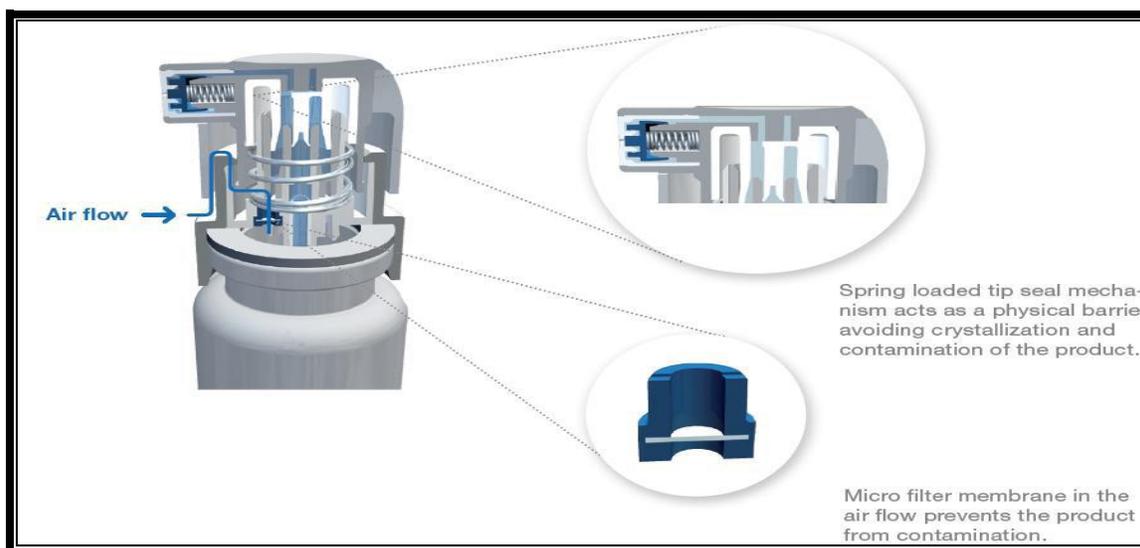


Fig. 4: Advanced preservative free Plus Container

Evaluation of Metered Dose Topical Spray Formulations

The quality control tests on the metered dose topical spray formulations are performed mainly to optimize the drug delivery systems and to improve the efficiency of delivery of the medicinal agent.

The metered dose topical spray formulations are evaluated on the basis of tests indicated for aerosol preparations as per monographs in IP, BP and USP [26]. Tests related to propellants are not carried out, as the developed metered dose topical spray formulations do not contain propellants in the system.

a. Viscosity

The viscosity of the solutions is measured at $25 \pm 1^\circ\text{C}$ using Brookfield viscometer. The spindle is rotated at 1 rpm.

b. Volume of solution delivered upon each actuation

The volume of solution delivered upon each actuation is calculated using eq. 1.

$$AL = (W_t - W_o) / D_n \dots\dots\dots (1)$$

Where AL is the volume of solution delivered upon each actuation, W_t is weight of formulation after actuation, W_o is the initial weight of the formulation before actuation, and D_n is the density of the formulation. An average weight of five actuations is calculated.

c. Spray angle

The method of impingement of spray on a piece of paper is used for the study. Sudan red (10 mg) is dissolved in formulation to facilitate visualization. The sprays are actuated in horizontal direction onto a white paper mounted at a distance of 15 cm from the nozzle. The radius of the circle, formed on the paper, is recorded in triplicate from different directions. Spray angle (θ) is calculated by eq. 2.

$$\text{Spray angle } (\theta) = \tan^{-1} (l/r) \dots\dots\dots (2)$$

Where 'l' is the distance of paper from the nozzle, and r is the average radius of the circle.

d. Spray Pattern

Characterization of spray pattern is important for evaluating the actuator, spray pump performance as well as deposition pattern of formulation. Spray pattern of the metered dose topical spray formulations is checked by

incorporating dilute solution of methylene blue in the formulation and spraying on a Whatmann paper placed at a definite distance. This paper is clipped on a board and the spray formulations are sprayed at the distance of 15cm. Whatmann paper is used for evaluating the spray pattern as dye gives a distinct blue coloration which shows the spray pattern on white background of Whatmann paper after application of the spray²⁷.

e. Evaporation time/ Film formation time

The evaporation time or time required for the spray film to dry is recorded. Time required for getting totally dry film is noted.

f. pH

The pH of the metered dose topical spray formulations are recorded by pH meter.

g. Ex- vivo Physical Evaluation

Placebo batches are actuated on left hand palms of three healthy human volunteers of 21–27 years in age, four times every 10 s from a distance of 15cm. Time required for film formation, appearance of film, flexibility of film, feeling of warmth and subsequent cooling sensation, irritation potential and water washability are recorded. The appearance of the film is graded as shiny and transparent (+) or shiny and translucent (++) or dull and opaque (+++). Dermal adhesion, flexibility and water washability of the film are graded as poor (+), moderate (++) or good (+++).

To check dermal adhesion of the film, the palms of each volunteer are rotated for 10 min in anti-clock wise direction with occasional opening and closing of palm, after 8min of actuation of the spray. During the study (720 min), the nature of the film is carefully evaluated for any fracture, separation or removal. After 720 min, water washability of the film is checked.

CONCLUSION

Topical drug delivery systems offer several advantages over oral delivery systems. This review explains added advantage of the novel drug delivery systems like the topical sprays using metered dose transdermal spray system. These topical spray formulations are easy to formulate and fabricate possessing targeted drug delivery, uniform dosing, patient compliance, aesthetic appeal, good efficacy and non irritancy. Such novel formulations can be a better future prospective in topical dosage forms over the conventional dosage forms.

REFERENCES

1. Guy RH. Current status and future prospects of transdermal drug delivery. *Pharm Res.* 1996; 13: 1765-1769.
2. Banker GBS and Rodes CT. *Modern Pharmacist*, 2 edition, Vol. 40, Marcel Dekker, New York, 1979: 263-273, 283,286-287,299-311.
3. Banker, GS and Chalmers RK. *Pharmaceutics and Pharmacy Practice*, I edition, Lippincott Company, 1982: 28-294.
4. Misra AN. *Controlled and Novel Drug Delivery*, CBS Publishers and Distributors, New Delhi, 1997: 107-109.
5. Kumari P, Shankar C and Mishra B. *The Indian Pharmacist*, June 2004; III: 7-16.
6. Jain S, Khare P, Gulbake A, Bansal D and Jain SK. *Drug Deliv.* 2010; 17: 443-51.
7. Segal M. *Patches, Pumps and Timed Release: New Ways to Deliver Drugs*. Food and Drug Administration. Retrieved on 2007-02-24.
8. Jarvinen A et al. Steady-state pharmacokinetics of Oestradiol gel in post-menopausal women: effects of application area and washing. *Br J Obstet Gynaecol.* 1997; 104, Suppl 16: 14-18.
9. Wang C, Burman N et al. Pharmacokinetics of transdermal Testosterone gel in hypogonadal men: application of gel at one site versus four sites: a general clinical research center study. *J Clin Endocrinol Metab.* 2000; 85(3): 964-9.
10. Lawrence M and Gareth D. Microemulsion-based media as novel drug delivery systems. *Adv Drug Deliv Rev.* 2000; 45: 89-121.
11. Roskos KV, Maibach HI and Guy RH. The effect of aging on percutaneous adsorption in man. *J Pharmacokinetic Biopharm.* 1989; 17(6): 617-30.
12. Reed JT et al. Skin type, but neither race nor gender, influences epidermal permeability barrier function. *Arch Dermatol.* 1995; 131(10): 1134-8.
13. Galer BS. Topical medications In: Loeser JD, Butler SH, Chapman CR, Turk DC, eds. *Bonica's Management of Pain*, 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins. 2001: 1736-1742.
14. Hedner T and Everts B. The early clinical history of salicylates in rheumatology and pain. *Clin Rheumatol.* 1998; 17(1): 17-25.
15. Morgan TM. Metered dose transdermal spray (MDTS), In: *Modified release drug delivery technology*, J. Hadgraft et al. Marcel Dekker, 2003 (126), 523-531.
16. Mukesh C and Stavan A et al. Fabrication of Modified Transport Fluconazole Transdermal Spray Containing Ethyl Cellulose and Eudragit® RS100 as Film Formers; *AAPS PharmSciTech.* 2009; 10(2): 684-691.
17. Sciarra JJ. Pharmaceutical aerosols, In: *Modern pharmaceuticals*, G.S. Banker, Rhodes christopher (Ed), 3rd Ed, Marcel Dekker, 1996; 72: 547-553.
18. Bakshi A, Bajaj A et al. A Novel Metered Dose Transdermal Spray Formulation for Oxybutynin, *Indian J Pharm Sci.* 2008; 70(6): 733-739.
19. Bakshi A, Bajaj G, Malhotra et al. A Novel Metered Dose Transdermal Spray Formulation for Oxybutynin. *Indian J Pharm Sci.* 2008; 70(6): 733-739.
20. Bandrup et al. *Handbook of polymers*, J. Willey publications. 1972: 214-227.
21. Jadupati M, Suma OS, Amit kumar N and Kalyan kumar S. Development and Evaluation of Microemulsions for Transdermal Delivery of Insulin. *International Scholarly Research Network ISRN Pharmaceutics.* 2010; 1-7.
22. Katzung BG and Furst DE. Non steroidal anti inflammatory drugs, disease modifying anti rheumatic drugs, non opioid analgesics, drugs used in gout. In: Katzung BG editor. *Basic and clinical pharmacology*, 7th ed., Appliton and Lang Stamford, Connecticut, 1998: 586, 1068.
23. Kaur IP and Smith LI. Percutaneous Absorption-Penetration Enhancers. 1998: 34-33.
24. Kaur Sukhbir, Kaur Navneet et al. Development of modified transdermal spray formulation of Psoralen extract; *Der Pharmacia Lettre.* 2013; 5(2): 85-94.
25. Khan M. Bioavailability of vitamin B12 using a small volume nebulizer ophthalmic drug delivery system. *Clin Exp Ophthalmol.* 2005; 33: 402-407.

26. Khanna Surabhi, Katara OP and Drabu Sushma. Lecithin based Microemulsions for topical delivery of Tretinoin. International Journal of Drug Development & Research. 2010; 2(4): 711-719.
27. Kikwai L, Kanikkannan N et al. Effect of vehicles on the transdermal delivery of melatonin across porcine skin *in vitro*. J Control Release. 2002; 83(2): 307-11.
28. www.apta.com.