JPR INFO .com
Journal of Pharma Research

Journal of Pharma Research
Available online through
www.jprinfo.com

Review Article
ISSN: 2319-5622

TRANSDERMAL GELS - A NOVEL APPROACH FOR DEVELOPMENT OF TRANSDERMAL DRUG DELIVERY SYSTEM

Awanika Shukla, Kapil Kumar*, SK. Padhy
Global Institute of Pharmaceutical Education and Research, Kashipur, U.K., INDIA.

Received on: 05-06-2016; Revised and Accepted on: 17-06-2016

ABSTRACT

Transdermal drug delivery systems are dosage forms that deliver a therapeutically effective amount of drug across a patient's skin. The delivery of drugs through the skin provides several important advantages over traditional oral and intravenous delivery routes. The ability to deliver drugs for systemic effect through intact skin while by passing first pass hepatic metabolism has accelerated transdermal drug delivery research in pharmaceutics. Transdermal delivery provides convenient and pain-free self-administration for patients. It eliminates frequent dosing administration and plasma level peaks and valleys associated with oral dosing and injections to maintain a constant drug concentration, and a drug with a short half-life can be delivered easily. Transdermal gels are semisolid formulations, which have an external solvent phase, may be hydrophobic or hydrophilic in nature, and are immobilized within the spaces of a three-dimensional network structure.

Keywords: *Transdermal Drug Delivery Systems, Transdermal Gel, First Pass Hepatic Metabolism.*

INTRODUCTION

Skin is the main route of topical drug delivery system one of the most readily accessible organs on human body for topical administration. Delivery of drugs through the skin has been an attractive as well as a challenging area for research. An optimum amount of the drug is administered to the patient with a motive to reaches exactly at the site of action and to produce therapeutic effects [1]. To minimize drug degradation and loss, to avoid harmful side-effects and to increase drug bioavailability various drug delivery and drug targeting systems are currently under development. One of the most often utilized method is transdermal delivery system that involves transport of therapeutic substances through the skin for systemic effect. The main purpose of transdermal drug delivery system is to deliver drugs to the systemic circulation through the skin at predetermined rate with minimum inter and intra patient variability [3].

Its discovery is a major breakthrough in the field of controlled drug delivery systems.

Transdermal gels are semisolid formulations, consisting of typically 99% weight liquid, which is immobilized by surface tension between it and a macromolecular network of fibers built from small amount of a gelating substances present, whenever used at pathological sites offer great advantage in a faster release of drug directly to the site of action, independent of water solubility of drug as compared to creams and ointments [4].

1. Transdermal drug delivery system:

Transdermal drug delivery systems are topically administered medicaments in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate [5].

Compared to other conventional routes of drug delivery such as oral, injection and inhaler, transdermal delivery has a variety of advantages. Transdermal systems are non-invasive, convenient, and inexpensive and can be self-administered. They can provide sustained plasma concentration profile for long periods of time [6]. A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medication. These devices allow for pharmaceuticals to be delivered across the skin barrier [7].

***Corresponding author:**
Kapil Kumar
Global Institute of Pharmaceutical Education and Research, Kashipur, U.K., INDIA.
**E-Mail: kapil5november@gmail.com*

1.2: Transdermal Gels:

The term 'gel' was introduced in the later 1800 to name some semisolid material according to pharmacological, rather than molecular criteria [8].

Gel are a semisolid system that contains either suspension of small inorganic particles or large organic molecules within the liquid. There is a liquid phase is constrained within a three dimensional polymeric matrix of natural or synthetic gums in which a high degree of physical or chemical cross linking is present. Gels contain substantially dilute cross-linked system, which shows no flow when in the steady state. Gels have higher aqueous component which allows greater dissolution of drugs, which in turn easily migrate the drug through a vehicle, compared to ointment and creams. Therefore, they are better in terms of use and patient compliance. Transdermal gels deliver a therapeutically effective amount of drug across a patient's skin. However both topical and transdermal gels are intended for external use [9]. Topical gels are intended for localized action on one or more layers of the skin whereas transdermal gels use the percutaneous route for systemic effect. Gel formulations provide faster drug release as compared to the ointments and creams in which the drug is dispersed as fine particles. Gels have a higher aqueous component that permits greater dissolution of drugs, and also permit easier movement of the drug through a vehicle that is essentially a liquid, compared with the ointment or cream bases [10].

2.1. Advantages of transdermal gels: [11, 12]

1. No first pass hepatic metabolism
2. In case of toxicity drug can be easily eliminated.
3. Reduce side effects.
4. Less dosing frequency.
5. Suitable for nonresponsive patients, unconscious or comatose patients.
6. Continuity of drug administration permitting the use of a drug with short biological half-life.
7. Drugs that are degraded by enzymes and acids in the gastrointestinal system can be administrated by transdermal gels.

2.2. Limitations of transdermal gels: [13]

1. Unsuitable for drugs that irritate or sensitize the skin.
2. Not suitable for drugs which have very low or high partition coefficient. Drug should have favorable partition coefficient (log P 1-3).
3. Not suitable for drug having larger molecular weight (>500Da), it becomes to penetrate the stratum cornea.
4. Not favorable for drugs which are extensively metabolized in skin.

2.3. Advantages of transdermal gels over transdermal patches: [14]

1. Due to heat, cold, and sweating patch may be removed from skin surface. Therefore a new patch has to be applied daily.
2. In case of no proper adherence of patch, there will be need of various types of tapes and bandages, but none of them will be satisfactory.
3. The patches may remove from skin by itself.
4. Patches applied on skin may cause bleeding and inflammation when applied or removed improperly. The skin beneath the skin patch becomes abraded and wet to tough.
5. Mostly patches depend on concentration gradient of drug within the matrix or reservoir to deliver drug through skin. As a result, a high percentage of dose can remain within the patch when delivery get stopped or slow down.

2.4. Classification of transdermal gels: [15, 16]

a) Based on nature of colloid phase:

i) Inorganic gels
ii) Organic gels

b) Based on nature of solvent:

i) Aqueous gels
ii) Non aqueous gels

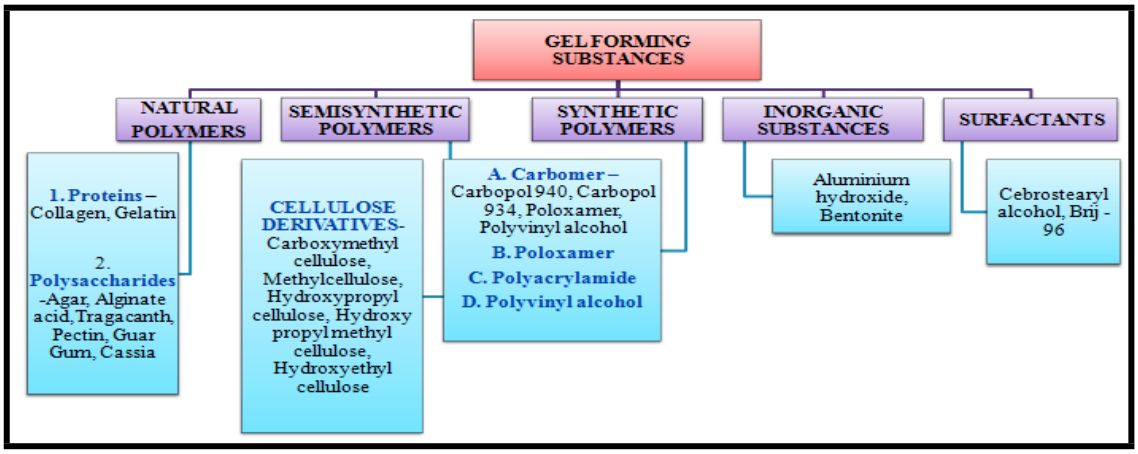
c) On the basis of structure:

Physical gels: unstable at high temperature or in solvents.

Chemical gels: not tough due to uneven temperature.

Slide ring gels: in that polymer chains are covalently cross did not link nor attractively interacted rather they are interlocked.

2.5. Gel forming substances: [17]



3. Stratum corneum as the transdermal permeation barrier:

The skin of an average adult body covers a surface area of approximately 2 sqm and receives about one–third of the blood circulation through the body. It is one of the most readily accessible organs on the human body [18].

The skin is a multilayered organ composing of many histological layers:

1. Epidermis; 2. Dermis; 3. Hypodermis

The outermost layer, the epidermis is approximately 100 to 150 micrometers thick has no blood flow and includes a layer within it known as the stratum corneum. This is the layer most important to transdermal delivery as its composition allows it to keep water within the body and foreign substances out. Beneath the epidermis, the dermis contains the system of capillaries that transport blood throughout the body [19]. If the drug is able to penetrate the stratum corneum, it can enter the blood stream. A process known as passive diffusion which occurs too slowly for practical use is the only means to transfer normal drugs across this layer [20].

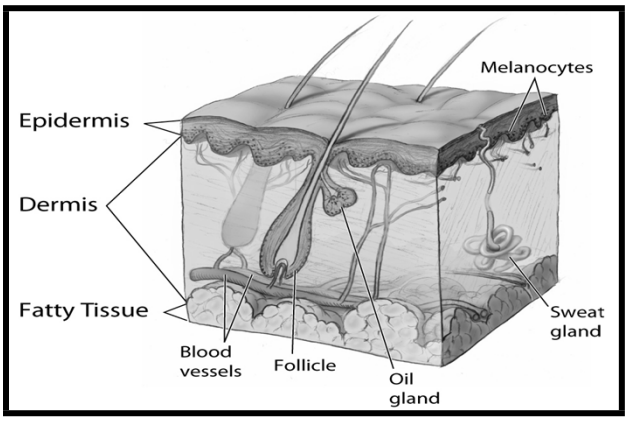


Fig. 1: Structure of Skin

4. Factors affecting transdermal permeation:

4.1. Biological factors:

1. Anatomic site: [21]

The skin absorption varies from site to site on the body. There is variability but, over most of the surface, this is not greater than the normal inter individual variability observed at a specific site. Certain regions are more permeable - the genitalia, especially the scrotum, the axilla, the face, the scalp, and post-auricularly.

2. Skin condition and disease: [22]

The intact, healthy skin is a tough barrier but many agents can damage it. Vesicants such as acids and alkalis injure barrier cells and thereby promote penetration. In case when the skin gets inflamed in a disease with loss of stratum corneum and altered keratinization, the permeability increases.

3. Age: [22]

Skin of the young and the elderly is more permeable than adult tissues. Children are more susceptible to the toxic effect of drugs and chemicals, due to their greater surface area per unit body weight.

4. Skin metabolism: [22]

Catabolic enzymes present in the viable epidermis may leads to a drug inactive by metabolism and affect the topical availability of the drug.

4.2. Physicochemical Factors:

1. Skin hydration: [23]

Water saturates the skin, the tissues swells, soften and wrinkles and thus increases its permeability. Skin hydration can be achieved simply by covering or occluding the skin with plastic sheet leading to accumulation of sweat and condensed water vapour.

2. Temperature: [23]

Increase in the skin temperature leads to increase in the rate of skin permeation due to rise in solubility of drug in skin tissues and increased dilation of skin vessels.

3. pH and pKa: [24]

Solutions having high pH values when applied to the skin, can be damaging to the skin. An ionizable drug will be present in both charged and uncharged form depending on its pK_a and pH of the environment. The ionized moiety on the other hand is usually less lipid soluble, limiting transdermal permeation.

4. Partition coefficient: [25]

Drugs would preferably have a balanced lipophilic/ hydrophilic character and a drug with a log P value of ≤ 2 is considered to be a potential candidate for transdermal delivery.

5. Evaluation parameters of transdermal gel:

1. Measurement of pH: [26]

The pH of various gel formulations is measured by means of digital pH meter. One gram of gel is dissolved in 100 ml distilled water and stored for two hours.

2. Drug content: [27]

1 g of the prepared gel is mixed with 100ml of suitable solvent. Aliquots of different concentration are prepared by suitable dilutions after filtering the stock solution and absorbance is measured by UV spectrophotometer.

3. Viscosity study: [28]

The measurement of viscosity of the transdermal gel is done with a Brookfield Viscometer. The gels are rotated at 0.3, 0.6 and 1.5 rotations per minute. At each speed, the corresponding dial reading is noted.

4. Spreadability: [29]

One of the criteria for a gel to meet the ideal quantities is that it should possess good spreadability. It is the term expressed to denote the extent of area to which gel readily spreads on application to skin or affected part. The therapeutic efficacy of a formulation also depends upon its spreading value. It is calculated by using the formula:

$$S = \frac{ML}{T}$$

Where M = wt. tied to upper slide, L = length of glass slides, T = time taken to separate the slides

5. Extrudability study: [30]

To determine Extrudability the formulations are filled in the collapsible tubes after the gels are set in the container. The extrudability of the formulation is determined in terms of weight in grams required to extrude a 0.5 cm. ribbon of gel in 10 second.

6. Skin irritation study: [31]

Guinea pigs (400-500 g) of either sex are used for testing of skin irritation. The animals are maintained on standard animal feed and had free access to water. The animals are kept under standard conditions. Hair is shaved from back of guinea pigs and area of 4 cm^2 is marked on both the sides, one side served as control while the other side is test. Gel is applied (500 mg / guinea pig) twice a day for 7 days and the site is observed for any sensitivity and the reaction if any, is graded as 0, 1, 2, 3 for no reaction, slight patchy erythema, slight but cofluent or moderate but patchy erythema and severe erythema with or without edema, respectively.

7. In vitro Diffusion studies: [32]

The diffusion studies of the prepared gels can be carry out in Franz diffusion cell for studying the dissolution release of gels through a cellophane membrane. Gel sample (0.5g) is taken in cellophane membrane and the diffusion studies are carried out at 37 ± 1° using 250 ml of phosphate buffer (pH 7.4) as the dissolution medium. Sample is withdrawn periodically and analyzed by UV spectrophotometer.

8. Stability: [33]

The stability studies are carried out for all the gel formulation by freeze - thaw cycling. Product is subjected to a temperature of 4° C for 1 month, then at 25°C for 1 month, then at 40°C for 1 month. After this gel is exposed to ambient room temperature and liquid exudates separating is noted.

9. Consistency: [33]

Consistency of the prepared gels is determined by dropping a cone attached to a holding rod from a fix distance of 10cm in such way that it should fall on the centre of the glass cup filled with the gel. The penetration by the cone is measured from the surface of the gel to the tip of the cone inside the gel. The distance traveled by cone is noted down after 10sec.

CONCLUSION

Transdermal drug delivery is an exciting and challenging area. Transdermal drug delivery systems are a constant source of interest because of the benefits that they afford in overcoming many drawbacks associated with other modes of drug delivery (i.e. oral, intravenous). There are numerous transdermal delivery systems currently available on the market. Avoidance of hepatic first-pass metabolism and the GI tract for poorly bioavailable drugs is another advantage of transdermal delivery. Elimination of this first-pass effect allows the amount of drug administered to be lower, and hence safer in hepatic-compromised patients, resulting in the reduction of adverse effects. Transdermal systems are generally inexpensive when compared with other therapies on a monthly cost basis, as patches are designed to deliver drugs from 1 to 7 days. The other advantage of transdermal delivery is that multiple dosing, on-demand or variable-rate delivery of drugs, is possible with the latest programmable systems, adding more benefits to the conventional patch dosage forms. The general acceptability of transdermal products by patients is very high, which is also evident from the increasing market for transdermal products.

ACKNOWLEDGEMENT

The authors are thankful to Dr AK Saxena, Ex-Chief Scientist and former Head, Division of Medicinal Chemistry, CDRI, Lucknow, India for their technical suggestion and motivation during the work.

REFERENCES:

1. Shingade. Review on: Recent Trend on Transdermal Drug Delivery System, Journal of Drug Delivery and Therapeutics, **2012**; 2(1):66-75.
2. Chien, YW. Novel Drug Delivery Systems, Drugs and the Pharmaceutical Sciences, Marcel Dekker, New York, **1992**; 50, 797.
3. Roberts MS. Targeted Drug Delivery to the skin and the deeper tissues: Role of Physiology, Solute Structure and Disease, Clin. Exp. Pharmacol, Physiol, **1997**; 2(11): 87-9.
4. Brahmankar DM. Biopharmaceutics and Pharmacokinetics, a Treatise, Vallabh Prakashan, Delhi, **2003**; 365-366.
5. Trottet L, Merly C, Mirza M, Davis AF. Effect of finite doses of propylene glycol on enhancement of in vitro percutaneous permeation of loperamide hydrochloride, Int. J. Pharm., **2004**; 2(4): 213-219.
6. Higuchi WI. Analisis of data on the medicament release from ointments, J. Pharm. Sci., **1962**; (51): 802-804.
7. Gupta GD, Gaud RS. Release rate of Nimesulide from different gellants, Ind. J. Pharm. Sci., **1999**; (61): 227-230.
8. Scheuplein RJ, Blank IH, Brauner GJ, MacFarlane DJ. Mechanism of precutaneous absorbtion. IV Penetration of nonelectrolytes (alcohols) from aqueous solutions and from pure liquids, J. Invest. Dermatol., **1969**; 52(1): 63-70.
9. Kapoor D, Patel M, Singhal M. Innovation in transdermal drug delivery system, Int. Pharma. Sci, **2011**; 1(1): 54-61.
10. Jain N K, Controlled and Novel drug delivery system. 1st Edn, CBS Publications, New Delhi, **1997**; 110-115.
11. Goyal S. Novel Anti-Inflammatory Topical Herbal Gels Containing Withania somnifera and Boswellia serrata, Int. J. Pharma. Biol. Archi., **2011**; 2(4): 1087-1094.
12. Sara M, Nevine S, Omaima N, Abdel Aziz A. Formulation of microemulsion gel systems for transdermal delivery of celecoxib: In vitro permeation, anti-inflammatory activity and skin irritation tests, Drug Discoveries and Therapeutics, **2010**; 4(6): 459-471.
13. Charles M, Simon J. Ketoprofen release from permeation across and rheology of simple gel formulation that stimulate increasing dryness, Int. J. pharm., **2003**; 268: 37-45.
14. Shivhare U, Jain K, Mathur V. Formulation, development and evaluation of diclofenac sodium gel using water soluble polycrylamide polymer, Digest. J. of Nanomaterials and Biostructures, **2009**; 4: 285-290.
15. Priyanka A, Biswajit M. Design, development, physicochemical, and in-vitro and in-vivo Evaluation of

transdermal patches containing Diclofenac Diethylammonium salt, J. Pharm. Sci., **2002**; 91(9).
16. Abdel-Mottaleb M, Mortada N, Elshamy A, Awad G: Preparation and evaluation of Fluconazole gels, Egypt. J. Biomed. Sci., **2007**; 23: 35-41.
17. Tayel S, Osman A. Formulation and evaluation of piroxicam gels. Egypt. J. Pharm. Sci., **1995**; 36: 1-14.
18. Pandit V, Khanum A, Bhaskaran S, Banu V. Formulation and Evaluation of transdermal films for the treatment of overactive bladder, Int. J. Pharm. Tech. Research, **2009**; 1(3): 799-804.
19. Jantharaprapap R, Stagni G. Effects of penetration enhancers on in vitro permeability of meloxicam gels, Int. J. Pharm., **2007**; 343: 26-33.
20. Arellano A, Santoyo S, Martin C, Ygartua P. Influence of propylene glycol and isopropyl myristate on the in vitro percutaneous penetration of diclofenac sodium from carbopol gels, Eur. J. Pharm. Sci., **1998**; 7: 129-135.
21. Karvana SY, Guneri P, Ertan G, Benzydamine hydrochloride buccal bioadhesive gels designed for oral ulcers: Preparation, rheological, textural, mucoadhesive and release properties, Pharm. Dev. Technol., **2009**; 14(6): 623-631.
22. Panchagnula R, Salve PS, Thomas NS, Jain AK, Ramarao P, Transdermal delivery of naloxone: effect of water, propylene glycol, ethanol and their binary combinations on permeation through rat skin, Int. J. Pharm., **2001**; 219: 95-105.
23. Loyd Allen V. Transdermals: Skin as a part of Drug Delivery System. Int. J. Pharma. Compounding, **2010**; 13(5): 75-80.
24. Singlavikas, Sainiseema, Singh gurpreet, Rana AC, Joshi Baibhav. Penetration enhancers: A novel strategy for enhancing trandermal drug delivery. Int. Res. J. Pharm., **2011**; 2(12): 32-36.
25. Gupta GD and Gaud RS. Release rate of Nimesulide from different gellants, Ind. J. Pharm. Sci., **1999**; 61: 227-230.
26. PathanInayat B, Setty CM. Chemical penetration enhancers for transdermal drug delivery systems, Tropical journal of pharmaceutical research, **2009**; 8(2): 173-179.
27. Gupta A, Mishra AK, Singh AK, Gupta V and Bansal P. Formulation and evaluation of topical gel of diclofenac sodium using different polymers. Drug Invention Today, **2010**; 2(5): 250-253.
28. Alsarra I, Bosela AA, Ahmed SM and Mahrous GM. Proniosomes as a drug carrier for transdermal delivery of ketorolac. Eur. J. Pharm. Biopharm., **2005**; 59: 485-490.
29. Nair R, Sevukarajan M, Mohammed B and Kumar J. Formulation of microemulsion based vaginal gel- in vitro and in vivo evaluation, Der Pharmacia Lettre, **2010**; 2(6): 99-105.
30. Sanjay, Jain BD, Padsalg A, Patel K, Mokale V, Formulation, development and evaluation of Fluconazole gel in various polymer bases, Asi. J. Pharm., **2007**; 1: 63-68.
31. Suvakanta D, Padala NM, Lilakanta N, Prasanta C. Kinetic modeling on drug release from controlled drug delivery systems, Acta Poloniae Pharmaceutica, **2010**; 67(3): 217-223.
32. Rogerson A, Cummings J, Willmott N and Florence AT. The distribution of doxorubicin in mice following administration in niosomes, J. Pharm. Pharmacol., **1988**; 40(5): 337-342.
33. Pershing LK, Lambert LD, Knutson K. Mechanismof a ethanol-enhanced estradiol permeation across human skin in vivo, Pharm. Res., **1990**; 7: 170-175.

How to cite this article:

Kapil Kumar et al., TRANSDERMAL GELS - A NOVEL APPROACH FOR DEVELOPMENT OF TRANSDERMAL DRUG DELIVERY SYSTEM, J. Pharm. Res., 2016; 5(6): 155-158.

Conflict of interest: The authors have declared that no conflict of interest exists.

Source of support: Nil