Available Online at www.jddt.in

ISSN: 2320 - 4230

Journal of Drug Discovery and Therapeutics 2 (20) 2014, 26-31

REVIEW ARTICLE

Topical gel: a novel approach for pain relief treatment

Rajesh Asija[1]*, Sangeeta Asija[1], Nitin Nama[1], Raj Singh Chauhan[1]

[1] Department of pharmaceutics, Maharishi Arvind institute of pharmacy, Mansarovar, Jaipur-302020, Rajasthan, India

Received 21 July 2014; Accepted 30 July 2014

ABSTRACT

The main advantage of topical delivery system is to bypass the first pass metabolism, avoidance of the risk and annoyance of intravenous therapy and of the varied conditions of absorption, like pH changes, gastric emptying time and presence of enzyme. Gel formulation provides better application property and stability in comparison to cream and ointment. Skin is one of the most extensive and readily accessible organs on human body for topical administration. Topical appliance of drugs offers probable advantages of delivering the drug directly to the site of action and acting for an extended period of time. The topical drug delivery scheme is generally used where the others system of drug administration fails or it is mainly used in contraception, urinary incontinence and pain management. This review describes the assorted formulation aspects, a variety of excipients, evaluation tests, challenges and drugs explored in the pasture of topical drug delivery.

Key Words: Topical gel, Skin, Urinary incontinence, Novel technology

INTRODUCTION:

Skin is one of the most readily accessible organs on human body for topical administration. Topical drug administration is a localized drug delivery system anywhere in the body through vaginal, ophthalmic, rectal and skin as topical routes. A typical human skin surface is known to include, on the normal 40-70 hair follicles and 200-300 sweat ducts on every square centimeter of the skin. Although skin has been separated histologically into the stratum corneum, the living epidermis and the dermis, together it can be considered a shield of barrier, permeation of this laminate can take place by diffusion via: Transcellular penetration (across the cells), Intracellular penetration (between the cells), Transappendageal penetration (via sweat, hair follicles and sebum glands).[1]

The U.S.P. defines gels as a semisolid system consisting of dispersion made up of either small inorganic particle or large organic molecule enclosing and interpenetrated by liquid. Gels consist of two phase system in which inorganic particles are not dissolved but merely dispersed throughout the continuous phase and large organic particles are dissolved in the continuous phase.[2]

Nowadays with reference to 74% of drugs are taken orally and are found not to be as effective as desired. Discovering a new medicine is a very expensive and time consuming process that makes re-designing the modules a more lucrative task. The design of dosage form, whether a tablet, an injection or a patch is to deliver the right amount of medicine at right time to the right target site and it becomes complicated if each medication were to be delivered in an optimal and preferred manner to the individual patient.[3] A continuous intravenous infusion is considered as a superior mode of drug administration as compared to oral route. However, to overcome the problems associated with intravenous infusion and to duplicate closely its benefits, skin is used as a most favorable part of drug administration. So, whilst skin is used as a part of drug administration. TDDS is a promising method of drug administration that can avoid the variability in rates of absorption and metabolism encountered in oral treatment.[4]

Gel formulation provides better application property and stability in comparison to cream and ointment. Topical gels are deliberate for skin application or to certain mucosal surfaces for local action or percutaneous penetration of medicament or for their emollient or defensive action.[5] Gels are evaluated by subsequent parameters such as pH, viscosity, grittiness drug content, spreadability, extrudability, homogeneity, skin irritation studies, in-vitro release, in Stability.[6] TDDS is also used to minimizing undesirable side effects and provides utilization of drugs with short biological half lives with narrow therapeutic window by improving physiological and pharmacological response.[7]

Permeation enhancers are used for improving transdermal drug delivery by reversibly reducing the barrier resistance. Their mechanisms include disruption

*Corresponding author: Dr. Rajesh Asija || E-mail: nitinnamas@gmail.com

of intercellular lipid and or keratin domains and tight junctions which results in enhanced drug partitioning into tissue or by altering thermodynamic activity of drug.[8] Terpenes are secondary metabolites that are mostly synthesized in plants.[9] Thousands of different terpenes (monoterepenes, sesquiterpenes and diterpenes) have been identified till date and many have been investigated as penetration enhancers due to their high lipophilicity. The mechanism of action of terpenes involves increasing one or more of the following effects: diffusion coefficient, partition coefficient, drug solubility, lipid extraction, macroscopic barrier perturbation and molecular orientation of terpenes molecule.[10] In recent years, many attempts have been made to investigate the use of terpenes as skin permeation enhancers including menthol, linalool, limonene and carvacrol to promote the transdermal transport of drugs including chiral agents.[11]

Ideal properties of topical gel:

- Should be inert, compatible with other additives
- Should be stable at storage condition
- Should be liberated from microbial contamination
- Should be retain all rheological properties of gel
- Should be economical and non-toxic
- Should be washable through water and free as of staining nature
- Should be convenient in managing and its application
- Should be passes properties such as thixotropic, emollient and greaseless.[12-15]

OBJECTIVE OF FORMULATION OF TOPICAL GEL:

Topical formulation can be used to**:** Manipulate the barrier function of the skin, for example, topical antibacterial and antibiotics help a damaged barrier to ward off contamination, sun screening agents and the horny film protect the viable tissues from U.V. radiation and emollient arrangements restore pliability to a shrunken horny layer. Direct drugs to the feasible skin tissues without via oral, systematic or further routes of therapy. For example, anti-inflammatory, antipruritic, anesthetic and antihistaminic drugs are to be delivered to viable epidermis and dermis.[16-20]

Classification of Topical Drug Delivery Systems:

Topical drug delivery system is classified on the basis of physical state as shown in table 1:- [21-25]

Table 1: Classification of TDDS

Physical state	Examples
Solid	Powder, Plaster, Aerosol
Liquid	Solution, Lotion, Liniment, Emulsion, Suspension, Aerosol, Lacquer
Semi-solid	Cream, Paste, Gel, Jelly, Suppository, Ointment

Factors affecting topical absorption of drugs:

Physical factor:

1. Partition coefficient
2. Molecular weight (< 500 dalton)
3. Degree of ionization
4. Effects of vehicle
5. Particle size
6. Polymorphism
7. Concentration
8. Drug solubility

Physiological factor:

1. Skin thickness
2. Density of hair follicles
3. Density of sweet glands
4. Blood flow
5. Hydration of skin
6. Inflammation of skin
7. Types if skin (i.e. dry or oily skin)
8. Skin pH
9. Lipid content[26-30]

Methods to enhance drug penetration & absorption:

1. Chemical enhancement
2. Physical enhancement
3. Biochemical enhancement
4. Supersaturation enhancement

Factors to be considered while choosing a topical preparation:

1. Irritation or sensitization potential
2. Match the type of preparation with the type of lesion
3. Match the type of preparation with the site
4. Effect of the vehicle
5. The medication should not affect the skin nature. [30-32]

Penetration enhancer:

Percutaneous absorption can be ornamental in two ways either by chemical enhancer or by physical method:-

Chemical penetration enhancer:

By characterization, a chemical skin penetration enhancer raises skin permeability by reversibly damaging or by

altering the physicochemical nature of the stratum corneum to reduce its diffusional resistance. Among the alteration are improved hydration of stratum corneum and a change in the structure of the lipids and lipoproteins in the intercellular channels through solvent action or denaturation.

These may suitably be classified beneath the following main heading:

Solvents:

They enhance penetration possibly by swelling the polar pathway. Examples include alcohols, ethanol, methanol and water; dimethyl sulfoxide, dimethyl acetamide, pyrrolidones- 2 -pyrrolidone, N-methyl, 2- pyrrolidone, laurocapram (Azone)

Surfactant:

They proposed to enhance polar pathway convey, particularly of hydrophilic drugs. Following surfactants are used commonly: [33-36]

Table 2: Example of Surfactant

Anionic surfactant	Dioctyl sulphosuccinate, Decodecylmethyl sulphoxide, Sodium lauryl sulphate etc.
Cationic surfactant	Octenidine dihydrochloride, Benzalkonium chloride, Cetrimonium bromide etc.
Nonionic surfactant	Pluronic F68, Pluronic F127 etc.

Physical method of topical drug delivery:

Intophorosis:

Intophorosis is a progression :or a technique involving the transport of ionic or charged molecules into a tissue by the passage of direct or periodic electric current through an electrolyte solution containing the ionic molecules to be delivered using an appropriate electrode polarity.

Electroporation:

The process involves the application of transient high voltage electrical pulse to cause rapid dissociation of the stratum corneum through which large and undersized peptides, oligonucleotides and supplementary drugs can exceed in considerable amounts. The revolutionize in the membrane involves structural arrangement and conductance leading to temporary loss of semi-permeability of cell membranes suggesting formation of pores.

Sonophoresis:

Sonophoresis involves the usage of the regularity ultrasound waves. The ultrasound relevance has resulted in permeation of low frequency ultrasound was shown to increase the permeability of human skin to many drugs including high molecular weight protein by several orders of magnitude.

Phonophoresis:

The movement of drugs through living intact skin and into soft tissues under the ultrasound perturbation is called phonophoresis. The performance involves placing an ultrasound-coupling agent on the skin over the area to be treated and massaging the area with an ultrasound source.

Vesicular concept:

Drug enclosed vesicle made from phospholipids and nonionic surfactants are used for transport of drug into and across the skin. The assorted vesicles used for this purpose are niosomes, liposomes and transferosome. The lipid vesicle serve as a rate limiting membrane barrier for system absorption of drug, non-hazardous penetration enhancers for drug, organic solvents for solubilization of weakly soluble drugs and can incorporate both hydrophillc and lipophillic drugs.

Microfabricated microneedles technology:

This technology employed micron-sized needles made silicon. These microneedles after incorporation into the skin create conduits for transfer of drug through the stratum corneum. The drug later than crossing stratum corneum diffuses rapidly through deeper tissues and taken up by capillaries for systemic adminitration.

Physicochemical properties of topical:

Release characteristics:

The mechanism of drug release depends on whether the drug molecules are dissolved or suspended in the delivery scheme. The interfacial partition coefficient of drug from delivery systems to the skin pH of the vehicle.

Composition of drug delivery system:

instance polyethylene glycols of low molecular weight reduce permeation.

Nature of vehicle:

Liphophilic vehicle amplify permeation where as lipophobic vehicle diminish permeation.[37-40]

Common Topical Ingredients:

Vehicle:

Hydrophobic vehicle:

- **Hydrocarbons:** Liquid petrolatum (liquid paraffin, paraffin oil), White petrolatum (Vaseline), Yellow petrolatum, Squalane (perhydrosqualene, spinacane)
- **Silicones:** Liquid polydimethylsiloxanes (dimethicone, medical grade silicone oil)
- **Alcohols:** Lauryl alcohols (1-dodecanol, dodecyl alcohols), Myristyl alcohols (tetradecanol, tetradecyl alcohols), Cetyl alcohols (hexadecanol, palmityl alcohols), Stearyl alcohols (stenol, cetosteryl alcohols), Oleyl alcohols (ocenol)
- **Sterols; sterol esters:** Lanolin (hydrous wool fat, lanum), anhydrous lanolin (wool fat, anhydrous lanum), Semi synthetic lanolin
- **Carboxylic acids:** Lauric acid, Myristic acid, palmitic acid, stearic acid, oleic acid
- **Esters; polyesters:** Ethylene glycol monoesters, Propylene glycol monoesters, Glyceryl monoesters, Sorbitol monoesters, Sorbitain monoesters, Sorbitol diesters, Glyceryl tristearate, Hydrogenated oils, Sulfated oils, Isopropyl myristate, Isopropyl palmitate.
- **Ethers; polyethers:** Polyethylene-polypropylene glycols (pluronics)

Water-miscible vehicle, co solvent

- **Polyols; polyglycols:** Glycerin (glycerol), Liquid polyethylene glycol, Solid polyethylene glycol (hard macrogol, carbowax), 1,2Phenols-hexanetriol, Sorbitol solution 70%
- **Esters; polyesters:** Polyoxyethylene sorbitain monoesters (stearate- tweens), Polyoxy ethylene sorbitan polyesters (tweens)
- **Ethers; polyethers:** Polyethylene glycol monocetyl ether (cetomacrogol 1000), Polyethylene-polypropylene glycols (pluronics)

Structural matrix former

Hydrocarbons: White petrolatum (petroleum jelly, vaseline), Yellow petrolatum (petroleum jelly), Paraffin, Microcrystalline wax Ceresin (mineral wax, purified ozokerite)

Silicones: Fumed silica (cab-O-sil), Bentonite (colloidal aluminum silicate), Veegum (colloidal magnesium aluminum silicate)

Polyols, polyglycols: Solid polyethylene glycol (hard macrogol, carbowax)

Alcohols: Cetyl alcohols (hexadecanol, palmityl alcohols), Stearyl alcohols (cetosteryl alcohols)

Sterols; sterol esters: Cholesterol (cholesterin), Lanolin (hydrous wool fat, lanum), anhydrous lanolin (wool fat, anhydrous lanum), Semi synthetic lanolin's

Carboxylic acids: Lauric acid, Myristic acid, palmitic acid, stearic acid, oleic acid

Esters; polyesters: Bees wax, Carnauba wax, Myricin, Cholesterol esters (stearate), Polyoxyethylene sorbitain, Monoesters (stearate- tweens), Hydrogenated oils

Suspending, jelling, or viscosity inducing agents:

Silicones: Fumed silica (cab-O-sil), Bentonite (colloidal aluminium silicate), Veegum (colloidal magnesium aluminium silicate)

Polycarboxylates; polysulfates: polysaccharides Agar, Carragen, Tragacanth, Methylcellulose, Hydroxy ethyl cellulose, Carboxy vinyl polymer, pectin, xanthan, polyacrylic acid

Others: Ethanolamin, Triethanolamin

Water-in-oil (w/o) emulsifier

Sterols; sterol esters: Cholesterol (cholesterin), Lanolin (hydrous wool fat, lanum), Anhydrous lanolin (wool fat, anhydrous lanum, agnin), Semi synthetic lanolin's

Carboxylic acids: Na+, K+, ethanolamin salts of Lauric acid, Myristic acid, palmitic acid, stearic acid, oleic acid

Ethers; polyethers: Polyethylene-polypropylene glycols (pluronics)

Oil-in-water (o/w) emulsifier:

Esters; polyesters: Polyoxyethylene sorbitain monoesters (stearate- tweens), Polyoxy ethylene esters (stearate-polyethylene glycol monoesters), Polyoxy ethylene sorbitan polyesters (tweens)

Ethers; polyethers: Polyethylene glycol monocetyl ether (cetomacrogol 1000), Polyethylene-polypropylene glycols (pluronics)

Others: Sodium lauryl sulfate, Borax (sodium borate), Ethanolamine, Triethanolamine

Preservative

Antimicrobial: Benzalkonium chloride, Benzoic acid, Benzyl alcohol, Bronopol, Chlorhexidine, Chlorocresol, Imidazolidinyl urea, Phenol, Phenoxyethanol, Potassium sorbate, Sorbic acid

Antioxidants: a-Tocopherol, Ascorbyl palmitate, Butylated hydroxyanisole, Sodium ascorbate

Chelating agents

Buffer: Citric acid and salts, Phosphoric acid and salts, Acetic acid, Triethanolamine, Boric acid.

Humectant: Glycerin (glycerol), Propylene glycol (E1520), Glyceryl triacetate (E1518), Sorbitol (E420), Polydextrose (E1200), Quillaia (E999), Lithium Chloride.

Sequestering antioxidant: Citric acid and salts, Ethylenediaminetetraacetic acid.[41- 45]

CONCLUSION:

Topical products used for the treatment of common skin infections. The gels play an important role in the topical drug delivery system. They avoid gastrointestinal drug

absorption difficulties caused by gastrointestinal ph and enzymatic activity and drug interaction with food and drinks. They have localised effect with the minimum side effects. They also avoid the first pass metabolism.

REFERENCES:

1. Kaur L. P., Guleri T. K., Topical Gel: A Recent Approach for Novel Drug delivery: Asi. J. Bio. Pharma. Sci. 3(17); 2013: 1-5
2. Goyal S, Sharma P, Ramchandani U, Shrivastava S.K. and Dubey P.K., Novel anti-inflammatory topical gels: Int. J. Pharma. Bio. Arc. 2(4); 2011: 1087-1094.
3. Jani R, Jani K., Setty C. Mallikarjuna, Patel D., Preparation and evaluation of topical gel Valdecoxib. Int. J. Pharm. Sci. Res. 2(1); 2010: 51-54.
4. Niyaz B.B., Kalyani P, Divakar G, Formulation and evaluation of gel containing fluconazole antifungal agent, Int. J. Drug Dev. Res. 3(4); 2011: 109-128
5. Kaur L. P., Garg R., Gupta G.D., Development and evaluation of topical gel of minoxidil from different polymer bases in application of alopecia, Int. J. Pharm. Sci. 2(3); 2010: 43-47.
6. Mikari B.V., Mahadik K.R., Korde S.A. Formulation and evaluation of topical liposomal gel for fluconazole. Ind. J .Pharm.Sci., 44(4); 2010: 324-325.
7. Shelkeet S. J. Topical gel: A novel approach for development of topical drug delivery system, Int. J. Pharm. Tech., Vol. 5 (3); 2013: 2739-2763.
8. Bharadwaj S., Gupta G.D., Sharma V.K., Topical Gel: A Novel approach for drug delivery, Chem. Bio. Phy. Sci. Vol 2; 2012: 856-868.
9. Chandel A., Parashar B., Gupta N., Kumar A., Sharma V., An overview on gel formulation, Int. J. Pharm. rev. Res. Vol 1; 2013: 18-22.
10. Roychowdhury S., Singh D.H., Gupta R., Manish D., A Review on Pharmaceutical gel, Int. J. Pharma. Res. Bio. 1(5); 2012: 21-36
11. Shembale A.I., Borale D.K., Lohiya R.T., Useful penetration enhancers for transdermal drug delivery ; A review, Int. J. Pharma. Res. Dev. 2(5); 2010: 1-5
12. Saroha K., Singh S., Agarwal A., Nanda S., Transdermal Gels- An alternative vehicle for drug delivery, Int. J. Pharm. Chem. Biol. Sci. 3(3); 2013: 495-503
13. Soni H., Singhai A.K., Formulation and development of hydrogel based system for effective delivery of Rutin, Int. J. App. Pharma. 3(1); 2013: 5-13
14. Lakshmi J., KumarB.A., Gupta S., Investigation of Microemulsion as a Potential Carrier for Advanced Transdermal Delivery: An Overview, Int. J. Pharm. Sci. Rev. Res. 20(2); 2013: 51-59
15. Sabale V., Vora S., Formulation and evaluation of microemulsion-based hydrogel for topical delivery, Int. J. Pharm. Inv. 2(3); 2012: 140–149.
16. Khan S., Solid lipid nanoparticles- A Review, Wor. J. Pharmacy Pharma. Sci. 1(1); 2012; 96-115
17. Garud A., Singh D., Garud N., Solid Lipid Nanoparticles (SLN): Method, Characterization and Applications-Review, Int. Curr. Pharma. J. 1(11); 2012: 384-393.
18. Kamble M.S., Vaidya K.K., Bhosale A.K., Chaudhari P.D., Solid lipid nanoparticles and nanostructured lipid carriers- An overview, Int. J. Pharm. Chem. Bio. Sci. 2(4); 2012: 681-691.
19. Sanap G.S., Mohanta G.S., Solid lipid nanoparticles-based hydrogel formulation for topical delivery of Miconazole nitrate, Int. J. Pharm. Bio. Sci. 4(2); 2013: 21–33
20. Nikhil A., Harikumar S.L., Nirmala, Topical Liposomal Gel-A Novel drug delivery system, Int. J. Res. Pharm. Chem. 2(2); 2012: 383-391.
21. Patel B.D., Patel D.V., Chavda J.R., Patel N.K., Lipogel-A Novel topical Liposomal drug delivery system, Inventi Impact-NDDS, Vol 2; 2013: 104-109.
22. Joshi B., Singh G., Rana A.C., Saini S., Singla V., Emulgel- A comprehensive review on recent advances in topical drug delivery, Int. Res. J. Pharmacy, 2(11); 2011: 66-67.
23. Lachman, L., Lieberman H.A., The Theory and Practice of Industrial Pharmacy,3rd Edn., Varghese Publishing house, 1990: 534-536, 479, 492-494, 502, 526-531, 548, 564, 584-585, 589, 615-618
24. Topical Drug Delivery Systems : A Review by shailesh, Pharmainfo.net, http://www.pharmainfo.net/reviews /topical-drug-delivery-systems-review 6(5); 2008: 1-36
25. Surver C. and Davis F.A., Bioaviability and Bioequivalence, In Walter, K.A. (Ed.), Dermatological and Transdermal Formulation, Marcal Dekker, INC. NewYork, 119, 2002: 403,323,326,327,403.
26. Stan-posthumd J.J., Vink J., Lecessies, Bruijn J.A., Topical Tretinoin Under Oocclusion on a Typical Navei, 1998: 548.
27. Ansel H.C., Allen L.V., “Pharmaceutical Dosage Forms and Drug Delivery System”, 7 edition, Lippincott Willams and Wilkens, Baltimore, 2000: 244-246,249-251, 253-255,264-265.
28. Banker G.B.S., Rodes C.T., “Modern Pharmacist”, 2 edition, Vol. 40, Marcel Dekker, New York, 1979: 263-273, 283,286-287,299-311.

29. Lemberger A.P., "A Hand Book of Non Prescription Drug", American Pharmaceutical Association, Washington, 1973: 161.

30. Banker G.S., Chalmers R.K., "Pharmaceutics and Pharmacy Practice", I edition, Lippincott Company, 1982: 28- 294.

31. Vyas S. and Khar R.K., "Controlled Drug Delivery-Concept and Advances", Vallabh Prakashan, 2002: 418-422.

32. Kaur I.P., Smith L.I., "Percutaneous Absorption-Penetration Enhancers", 1998; 34-33.

33. Shah V.P., Williams R.L.,"Skin Penetration Enhancement Clinical Pharmacological and Regulatory Considerations", 1993: 27-35.

34. Stillwell G.K., "Electrical Stimulation and Iontophoresis in Krussen F.H.", Saunders Company, 1971: 14

35. Prausnitz M.R. and Bose V.G., "Electroporation: In Percutaneous Penetration Enhancers", CRC Press, Bocaraton. 1995: 393-405

36. Block L.H. " Remington -The Science and Practice of Pharmacy", I volume, 21 edition, Lippincott Williams and Wilkins, 2006: 875-877

37. Myers D., "Surfactant Science and Technology", VCH Publishers, 1992: 209-247.

38. Eccleston G.M., "Encyclopedia of Pharmaceutical Technology", Vol. 9, Marcel Dekker, New York, 1992: 375-421.

39. Walters K.A., "Percutaneons Absorption and Transdermal Therapy", Pharm. Tech., 1986: 30-42.

40. Gupta G.D., Gaud R.S., "The Indian Pharmacist", 2005: 69-76

41. Reddy M.S., Mutaliks, Rao G.V., "Preparation and Evalution of Minoxidil Gels for Topical Application in Absorption, Ind.J. Pharm. Sci.", 68(4); 2006: 432-436

42. Martin A., "Physical pharmacy", 4 edition, 1996: 423-431

43. Kanig J. and Mintzer H, "Measurement of Particulars Solid in Aerosal Systems Aerosal Technicoment", Vol III (2); 1960: 1

44. Johnson M.A., Darland W.E., Dorland E.K. "The Aerosal Handbook", 1972: 377

45. Gaur P.K., Mishra S, Purohit S, Transdermal drug delivery system A review , Vol. 2; 2009: 14-20

