BAOJ Pharmaceutical Sciences

Mohammad Javed Ansari, BAOJ Pharm Sci 2017, 3: 3
3: 040

Mini Review

Transdermal Drug Delivery Systems: An Emerging Non-Invasive Alternative to Oral and Parenteral Drug Administrations

Mohammad Javed Ansari*

Department of Pharmaceutics, College of Pharmacy, Prince Sattam Bin Abdul Aziz University, Al-Kharj, Saudi Arabia

Abstract

Transdermal drug delivery system (TDDS) is one of the widely studied non-invasive delivery system alternative to invasive parenteral delivery. It is also a preferred route for drugs having poor or inconsistent oral bioavailability due to extensive pre-systemic metabolism/elimination. TDDS overcomes the problems associated with painful parenteral drug delivery as well as unsuccessful oral drug delivery. It decreases adverse effects, improves efficacy and patient compliance. However, a very few number of drugs with low dose, low molecular weight and high octanol-water partition coefficients can only be successfully delivered by transdermal route, because of the anatomical structure of the barrier layer of skin. To achieve successful transdermal drug delivery, enhancement of skin permeability is of prime concern. Recently several physical, electrical, chemical and biochemical techniques have been proposed to increase the permeability of the skin. Among these, modification of permeability by chemical method is most widely used as it is economical, simple and rapid. Chemical permeation enhancers either improve the solubility or partition coefficient or increase the diffusion of drugs across the skin. However, these may be toxic and irritants to skin. Therefore, natural compounds such as essential oils, terpenes, fatty acids and alcohols has been proposed as safe and non-irritant skin permeation enhancers to improve the effectiveness of transdermal delivery systems.

Keywords: Transdermal Drug Delivery; Non-Invasive Technique; First Pass Effect

Transdermal Drug Delivery Systems: Opportunities and Challenges

Oral route of drug administration is the simplest and widely used route of drug therapy owing to ease of administration, possibility of self-administration, high degree of patient compliance [1-3]. however, it is not always feasible, as a large proportion of drugs are poorly water soluble thus requiring special technique to deliver the drug per oral [4-8]. Furthermore, many oral drugs fail to achieve sufficient plasma concentration which is clinically significant for therapeutic actions owing to gastric/intestinal degradation [9-11], poor intestinal absorption / permeability [12-14], pre-systemic gut/intestinal metabolism of drugs [15-20], counter-transport processes [21-24] or extensive hepatic first-pass elimination [25-30]. Consequently, incomplete or poor bioavailability necessitates frequent dosing leading to various adverse effects [31]. Such drug candidates which have poor performance upon oral administration usually belong to either class II or IV as per biopharmaceutical classification systems [32,33]. The drug candidates in these classes are well known as problematic drugs and these can be delivered successfully only when formulated as parenteral dosage forms [34-36]. Parenteral dosage forms are not only a valuable means to deliver problematic drugs successfully but are also the fastest acting dosage forms therefore are lifesaving and very valuable in emergency situations [37,38]. However, unfortunately, it is also one of the least acceptable dosage forms owing to its invasiveness nature and several associated complications. Pain / abscess formation at the site of injection, cross infections, chances of thrombophlebitis, embolism, acute idiosyncratic reactions, chances of improper dosing, adverse reactions, inability of dosage withdrawal are some of the problems associated with parenteral therapy [39-53].

Currently the pharmaceutical industries are focusing on the development of transdermal drug delivery systems (TDDS) due to several advantages including its site–specificity, non- invasiveness, dosage withdrawal capacity, zero first – pass effect and constant drug levels in the blood [54-58]. All of the above features help in ease of administration, reducing adverse effects, improving efficacy

***Corresponding author:** Mohammad Javed Ansari, Department of Pharmaceutics, College of Pharmacy, Prince Sattam Bin Abdul Aziz University, Al-kharj, Saudi Arabia, Tel: +96615886041; Fax: +9661588600; E-mail: javedpharma@gmail.com

Sub Date: June 6, 2017, **Acc Date:** July 10, 2017, **Pub Date:** July 10, 2017.

Citation: Mohammad Javed Ansari (2017) Transdermal Drug Delivery Systems: An Emerging Non-Invasive Alternative to Oral and Parenteral Drug Administrations. BAOJ Pharm Sci 3: 040.

and patient compliance leading to cost effective treatment [59-62]. Therefore, transdermal delivery has emerged as one of the best alternatives of invasive parenteral delivery and unsuccessful oral delivery of drugs due to associated problems such as extensive first pass metabolism, instability in gastrointestinal tract and incomplete absorption etc.. However, it is interesting to note that all drug candidates cannot be delivered successfully through transdermal route due to anatomical and physiological constraints of skin [63]. The appropriate drug features for TDDS includes low dose, low molecular weight and high octanol-water partition coefficients [64]. All of these limitations or preconditions result in relatively less number of approvals of transdermal products thus less market shares in comparison to the oral drug products [65-67]. The first generation of transdermal delivery systems included transdermal patches which were generally composed of either a simple matrix of drug reservoir in adhesive layer which rest on skin or a rate limiting semi permeable membrane separating the drug reservoir and adhesive layer. Some of the transdermal patches approved for clinical use includes drugs such as buprenorphine, clonidine, estradiol, fentanyl, nitroglycerine, scopolamine, selegeline, testosterone, lidocaine, epinephrine, menthol, diclofenac, capsaicin etc [51]. These systems were able to deliver incorporated drugs at controlled rates for prolonged durations such over days or weeks thus these were preferred over oral drugs requiring frequent dosing.

Barrier nature of skin's stratum corneum was main challenge for transdermal delivery of variety of drug molecules. Several techniques to enhance the permeability of stratum corneum in order to deliver different drug molecules, lead to development of the second generation of transdermal delivery systems. Strategies to combat the barrier nature of skin to increase its permeability include physical / electrical, chemical and biochemical techniques. Iontophoresis (application of electrical current to enhance delivery small charged molecules via electrophoresis) and sonophoresis (application of ultrasound to the skin that causes cavitations, thermal effects, and mechanical perturbation of the stratum corneum) are some of the popular physical methods along with use of chemical permeation enhancers (application of chemicals that intercalate with the lipid bilayers thus change the fluidity of skin) to enhance the skin permeability of the drugs [55,68-78]. Both physical as well as chemical methods of enhancing permeability of stratum corneum suffers with limitations such as skin irritation, pain, and injury to deeper tissues. However latter method finds wider acceptability as it is economical, simple, rapid, and several natural non-irritating penetration enhancers such as essential oils, terpenes and peptides have been employed as safe penetration enhancers [79-81]. Transdermal delivery of macromolecules and hydrophilic molecules warranted development of third generation transdermal delivery techniques such as microneedles (hollow microneedle carriers fabricated from silicon, metal, sugar, or plastic in groups of 150-650 microneedles/ cm^2 called arrays), [82-84] skin electroporation (application of high voltage pulses to cause temporary structural perturbation of lipid bilayer in the skin), [85] and thermal ablation (application of heat to the skin for very short periods of time like for micro- to milliseconds that forms painless, reversible microchannels in the stratum corneum without damaging the underlying tissue) [86].

Conclusion

Transdermal drug delivery has emerged as viable alternative to invasive parenteral drug delivery systems and drugs having extensive first pass metabolism, however, barrier nature of staratum corneum and pre-requisite physicochemical properties of drug candidates has been main challenges to commercialization of products based on transdermal drug delivery. Nevertheless ongoing extensive research into active technologies such as iontophoresis, sonophoresis, skin electroporation, thermal ablation, micro needles and combinations of natural penetration enhancers to overcome the barrier nature of skin, has great potential for growth and commercialization of transdermal delivery market.

References

1. Amidon GL, Lennernäs H, Shah VP, Crison JR (1995) A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharmaceutical research 12(3): 413-20.
2. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ (1997) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Advanced drug delivery reviews 23(1-3): 3-25.
3. Lipinski CA (2002) Poor aqueous solubility-an industry wide problem in drug discovery. Am Pharm Review 5(3): 82-85.
4. Stegemann S, Leveiller F, Franchi D, De Jong H, Lindén H (2007) When poor solubility becomes an issue: from early stage to proof of concept. European journal of pharmaceutical sciences 31(5): 249-261.
5. Aungst BJ (2017) Optimizing Oral Bioavailability in Drug Discovery: An Overview of Design and Testing Strategies and Formulation Options. Journal of pharmaceutical sciences 106(4): 921-929.
6. Granero GE, Amidon GL (2006) Stability of valacyclovir: implications for its oral bioavailability. International journal of pharmaceutics 317(1): 14-18.
7. Bhattarai S, Tran VH, Duke CC (2007) Stability of [6]-gingerol and [6]-shogaol in simulated gastric and intestinal fluids. Journal of pharmaceutical and biomedical analysis. 45(4): 648-653.
8. Shah S, Qaqish R, Patel V, Amiji M (1999) Evaluation of the factors influencing stomach-specific delivery of antibacterial agents for Helicobacter pylori infection. Journal of pharmacy and pharmacology 51(6): 667-672.

9. Manach C, Williamson G, Morand C, Scalbert A, Rémésy C (2005) Bioavailability and bioefficacy of polyphenols in humans .I. Review of 97 bioavailability studies. The American journal of clinical nutrition 81(1): 230S-242S.

10. Zhao YH, Le J, Abraham MH, Hersey A, Eddershaw PJ, et al. (2001) Evaluation of human intestinal absorption data and subsequent derivation of a quantitative structure–activity relationship (QSAR) with the Abraham descriptors. Journal of pharmaceutical sciences 90(6): 749-784.

11. Thanou M, Verhoef JC, Junginger HE (2001) Chitosan and its derivatives as intestinal absorption enhancers. Advanced drug delivery reviews 50 Supp 1: S91-101.

12. Benet LZ, Wu CY, Hebert MF, Wacher VJ (1996) Intestinal drug metabolism and antitransport processes: A potential paradigm shift in oral drug delivery. Journal of controlled release 39(2-3): 139-143.

13. Hartiala KA (1973) Metabolism of hormones, drugs and other substances by the gut. Physiological reviews 53(2): 496-534.

14. Scheline RR (1968) Drug metabolism by intestinal microorganisms. Journal of pharmaceutical sciences 57(12): 2021-37.

15. Krishna DR, Klotz U (1994) Extrahepatic metabolism of drugs in humans. Clinical pharmacokinetics 26(2): 144-160.

16. George CF (1981) Drug metabolism by the gastrointestinal mucosa. Clinical pharmacokinetics 6(4): 259-274.

17. Yang J, Jamei M, Yeo KR, Tucker GT, Rostami-Hodjegan A (2007) Prediction of intestinal first-pass drug metabolism. Current drug metabolism 8(7): 676-684.

18. Wu CY, Benet LZ (2005) Predicting drug disposition via application of BCS: transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system. Pharmaceutical research 22(1): 11-23.

19. Chan LM, Lowes S, Hirst BH (2004) The ABCs of drug transport in intestine and liver: efflux proteins limiting drug absorption and bioavailability. European journal of pharmaceutical sciences 21(1): 25-51.

20. Sparreboom A, Van Asperen J, Mayer U, Schinkel AH, Smit JW, et al. (1997) Limited oral bioavailability and active epithelial excretion of paclitaxel (Taxol) caused by P-glycoprotein in the intestine. Proceedings of the National Academy of Sciences 94(5): 2031-2035.

21. Okudaira N, Tatebayashi T, Speirs GC, Komiya I, Sugiyama Y (2000) A study of the intestinal absorption of an ester-type prodrug, ME3229, in rats: active efflux transport as a cause of poor bioavailability of the active drug. Journal of Pharmacology and Experimental Therapeutics 294(2): 580-587.

22. Wu B, Kulkarni K, Basu S, Zhang S, Hu M (2011) First-pass metabolism via UDP-glucuronosyltransferase: a barrier to oral bioavailability of phenolics. Journal of pharmaceutical sciences. 100(9): 3655-3681.

23. Bardelmeijer HA, Ouwehand M, Buckle T, Huisman MT, Schellens JH, et al. (2002) Low systemic exposure of oral docetaxel in mice resulting from extensive first-pass metabolism is boosted by ritonavir. Cancer research 62(21): 6158-6164.

24. Lee MG, Chiou WL (1983) Evaluation of potential causes for the incomplete bioavailability of furosemide: gastric first-pass metabolism. Journal of Pharmacokinetics and Pharmacodynamics 11(6):623-640.

25. Blaschke TF, Rubin PC (1979) Hepatic first-pass metabolism in liver disease. Clinical pharmacokinetics 4(6): 423-432.

26. Kwan KC (1997) Oral bioavailability and first-pass effects. Drug metabolism and disposition 25(12): 1329-1336.

27. Pond SM, Tozer TN (1984) First-pass elimination. Basic concepts and clinical consequences. Clinical pharmacokinetic 9(1): 1-25.

28. Claxton AJ, Cramer J, Pierce C (2001) A systematic review of the associations between dose regimens and medication compliance. Clinical therapeutics 23(8): 1296-1310.

29. Chavda H, Patel C, Anand I (2010) Biopharmaceutics classification system. Systematic reviews in pharmacy 1(1): 62-69.

30. Kawabata Y, Wada K, Nakatani M, Yamada S, Onoue S (2011) Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: basic approaches and practical applications. International journal of pharmaceutics 420(1): 1-10.

31. Merisko-Liversidge E, Liversidge GG (2011) Nanosizing for oral and parenteral drug delivery: a perspective on formulating poorly-water soluble compounds using wet media milling technology. Advanced drug delivery reviews 63(6): 427-440.

32. Fahr A, Liu X (2007) Drug delivery strategies for poorly water-soluble drugs. Expert opinion on drug delivery 4(4): 403-416.

33. Shegokar R, Müller RH (2010) Nanocrystals: industrially feasible multifunctional formulation technology for poorly soluble actives. International Journal of Pharmaceutics 399(1): 129-139.

34. Lin RY, Pesola GR, Bakalchuk L, Heyl GT, Dow AM, et al. (1999) Rapid improvement of peak flow in asthmatic patients treated with parenteral methylprednisolone in the emergency department: a randomized controlled study. Annals of emergency medicine 33(5): 487-494.

35. Rossing TH, Fanta CH, Goldstein DH, Snapper JR, McFadden Jr ER (1980) Emergency Therapy of Asthma: Comparison of the Acute Effects of Parenteral and Inhaled Sympathomimetics and Infused Aminophylline 1–3. American Review of Respiratory Disease 122(3): 365-371.

36. Hanke CW, Higley HR, Jolivette DM, Swanson NA, Stegman SJ (1991) Abscess formation and local necrosis after treatment with Zyderm or Zyplast collagen implant. Journal of the American Academy of Dermatology 25(2 pt 1): 319-326.

37. Birrer GA, Murthy SS, Liu J, Estrada J (2001) Parenteral dosage forms. Separation Science and Technology 3: 269-305.

38. Lupton JR, Alster TS (2000) Cutaneous hypersensitivity reaction to injectable hyaluronic acid gel. Dermatologic surgery 26(2): 135-137.

39. Schanz S, Schippert W, Ulmer A, Rassner G, Fierlbeck G (2002) Arterial embolization caused by injection of hyaluronic acid (Restylane®). British Journal of Dermatology 146(5): 928-929.

40. Tice TR, Tabibi ES (1991) Parenteral drug delivery: injectables. Treatise on controlled drug delivery: fundamentals optimization, applications, Marcel Dekker, New York 2: 315-319.

41. Falchuk KH, Peterson L, McNeil BJ (1985) Microparticulate-induced phlebitis: its prevention by in-line filtration. New England Journal of Medicine 312(2): 78-82.

42. Quercia RA, Hills SW, Klimek JJ, Mclaughlin JC, Nightingale CH, et al. (1986) Bacteriologic contamination of intravenous infusion delivery systems in an intensive care unit. The American journal of medicine 80(3): 364-368.

43. Parker SE, Davey PG (1992) Pharmacoeconomics of intravenous drug administration. Pharmacoeconomics 1(2): 103-115.

44. Tjon JA, Ansani NT (2000) Transdermal nitroglycerin for the prevention of intravenous infusion failure due to phlebitis and extravasation. Annals of Pharmacotherapy 34(10): 1189-1192.

45. Hippalgaonkar K, Majumdar S, Kansara V (2010) Injectable lipid emulsions-advancements, opportunities and challenges. Aaps Pharmscitech 11(4): 1526-1540.

46. Johnson JL, He Y, Yalkowsky SH (2003) Prediction of precipitation-induced phlebitis: A statistical validation of an in vitro model. Journal of pharmaceutical sciences 92(8): 1574-1581.

47. Wysowski DK, Swartz L, Vicky Borders-Hemphill B, Goulding MR, Dormitzer C (2010) Use of parenteral iron products and serious anaphylactic-type reactions. American journal of hematology 85(9): 650-654.

48. Wilson JP, Solimando Jr DA, Edwards MS (1986) Parenteral benzyl alcohol-induced hypersensitivity reaction. Drug intelligence & clinical pharmacy 20(9): 689-691.

49. Critchley J, Dundar Y (2007) Adverse events associated with intravenous iron infusion (low-molecular-weight iron dextran and iron sucrose): a systematic review. Transfusion Alternatives in Transfusion Medicine 9(1): 8-36.

50. Bircher AJ, Auerbach M (2014) Hypersensitivity from intravenous iron products. Immunology and allergy clinics of North America 34(3): 707-723.

51. Prausnitz MR, Langer R (2008) Transdermal drug delivery. Nature biotechnology 26(11): 1261-1268.

52. Prausnitz MR, Mitragotri S, Langer R (2004) Current status and future potential of transdermal drug delivery. Nature reviews Drug discovery 3(2): 115-124.

53. Merino V, Alberti I, Kalia YN, Guy RH (1997) Transdermal and skin-targeted drug delivery. Journal of Cutaneous Medicine and Surgery 2(2): 108-119.

54. Brown MB, Martin GP, Jones SA, Akomeah FK (2006) Dermal and transdermal drug delivery systems: current and future prospects. Drug delivery 13(3): 175-187.

55. Barry BW (2001) Novel mechanisms and devices to enable successful transdermal drug delivery. European journal of pharmaceutical sciences 14(2): 101-114.

56. Ramesh P (1997) Transdermal delivery of drugs. Indian journal of pharmacology 29(3): 140-156.

57. Berner B, John VA (1994) Pharmacokinetic characterisation of transdermal delivery systems. Clinical pharmacokinetics 26(2): 121-134.

58. Wasley MA, McNagny SE, Phillips VL, Ahluwalia JS (1997) The cost-effectiveness of the nicotine transdermal patch for smoking cessation. Preventive medicine 26(2): 264-270.

59. Stapleton JA, Lowin A, Russell MA (1999) Prescription of transdermal nicotine patches for smoking cessation in general practice: evaluation of cost-effectiveness. The Lancet 354(9174): 210-215.

60. Bouwstra JA, Honeywell-Nguyen PL, Gooris GS, Ponec M (2003) Structure of the skin barrier and its modulation by vesicular formulations. Progress in lipid research 42(1): 1-36.

61. Naik A, Kalia YN, Guy RH (2000) Transdermal drug delivery: overcoming the skin's barrier function. Pharmaceutical science & technology today 3(9): 318-326.

62. Verma RK, Garg S (2001) Drug delivery technologies and future directions. Pharmaceutical Technology 25(2): 1-4.

63. Bracht S, Therapie-Systeme LL (2000) Transdermal therapeutic systems: a review. Innovations in Pharmaceutical Technology 6: 92-98.

64. Colombo P, Sonvico F, Colombo G, Bettini R (2009) Novel platforms for oral drug delivery. Pharmaceutical research 26(3): 601-611.

65. Alexander A, Dwivedi S, Giri TK, Saraf S, Saraf S, et al. (2012) Approaches for breaking the barriers of drug permeation through transdermal drug delivery. Journal of Controlled Release 164(1): 26-40.

66. Dhamecha DL, Rajendra VB, Rathi AA, Ghadlinge SV, Saifee M, et al. (2010) Physical approaches to penetration enhancement. International Journal of Health Research 3(2): 57-70.

67. Mathur V, Satrawala Y, Rajput M (2010) Physical and chemical penetration enhancers in transdermal drug delivery system. Asian journal of pharmaceutics 4(3): 173.

68. Benson HA (2005) Transdermal drug delivery: penetration enhancement techniques. Current drug delivery 2(1): 23-33.

69. Sinha VR, Kaur MP (2000) Permeation enhancers for transdermal drug delivery. Drug development and industrial pharmacy 26(11): 1131-1140.

70. Finnin BC, Morgan TM (1999) Transdermal penetration enhancers: applications, limitations, and potential. Journal of pharmaceutical sciences 88(10): 955-958.

71. Merino V, Castellano AL, Delgado-Charro MB (2017) Iontophoresis for Therapeutic Drug Delivery and Non-invasive Sampling Applications. Percutaneous Penetration Enhancers Physical Methods in Penetration Enhancement : 77-101.

72. Mitragotri S (2017) Sonophoresis: Ultrasound-Mediated Transdermal Drug Delivery. Percutaneous Penetration Enhancers Physical Methods in Penetration Enhancement : 3-14.

73. Rangsimawong W, Opanasopit P, Rojanarata T, Panomsuk S, Ngawhirunpat T (2017) Influence of sonophoresis on transdermal drug delivery of hydrophilic compound-loaded lipid nanocarriers. Pharmaceutical development and technology 22(4): 597-605.

74. Nguyen HX, Banga AK (2017) Fabrication, characterization and application of sugar microneedles for transdermal drug delivery 8(5): 249-264.

75. Medi BM, Layek B, Singh J (2017) Electroporation for Dermal and Transdermal Drug Delivery. Percutaneous Penetration Enhancers Physical Methods in Penetration Enhancement : 105-122.

76. Pathan IB, Setty CM (2009) Chemical penetration enhancers for transdermal drug delivery systems. Tropical Journal of Pharmaceutical Research 8(2): 173-179.

77. Kumar S, Tyagi LK, Chandra A (2011) Chemical penetration enhancers: an approach for better trancdermal drug delivery. Int J Pharm Res Dev 3(7): 87-95.

78. Ahmed BM, Sushma S (2015) Chemical permeation enhancement through skin. International Journal of Advanced Research 3(8): 644-651.

79. Saini S, Baghel SC, Agarwal SS (2014) Recent development in penetration enhancers and techniques in transdermal drug delivery system. Journal of Advanced Pharmacy Education & Research 4(1): 31-40.

80. Aggarwal S, Agarwal S, Jalhan S (2013) Essential oils as novel human skin penetration enhancer for transdermal drug delivery: a review. Int J Pharm Bio Sci 4(1):857-868.

81. Aqil M, Ahad A, Sultana Y, Ali A (2007) Status of terpenes as skin penetration enhancers. Drug discovery today 12(23): 1061-1067.

82. Lee JW, Park JH, Prausnitz MR (2008) Dissolving microneedles for transdermal drug delivery. Biomaterials 29(13): 2113-2124.

83. Kalluri H, Banga AK (2009) Microneedles and transdermal drug delivery. Journal of Drug Delivery Science and Technology 19(5): 303-310.

84. Sivaraman A, Banga AK (2017) Novel in situ forming hydrogel microneedles for transdermal drug delivery. Drug delivery and translational research 7(1): 16-26.

85. Marwah H, Garg T, Goyal AK, Rath G (2016) Permeation enhancer strategies in transdermal drug delivery. Drug delivery 23(2): 564-578.

86. Sintov AC, Hofmann MA (2016) A novel thermo-mechanical system enhanced transdermal delivery of hydrophilic active agents by fractional ablation. International journal of pharmaceutics 511(2): 821-830.