

Fabrication of two-layer dissolving polymeric microneedle patches for transdermal delivery of insulin in diabetic mice

陳佳欣 (5113)

2019/11/06

Outline

1. Introduction
2. Formulation of two-layer dissolving polymeric microneedle patches for insulin transdermal delivery in diabetic mice
3. Fabrication of two-layer dissolving polyvinylpyrrolidone microneedles with different molecular weights for in vivo insulin transdermal delivery
4. Conclusion

Abstract

Dissolving microneedle (MN) has been developed to overcome the stratum corneum barrier of skin, which allows the penetration of epidermis and enhance the transdermal delivery of insulin. The aim of this report was to investigate the fabrication of two-layer MN by two step casting method and centrifuging process to localize the drugs in the needles. Furthermore, the ex vivo and in vivo transdermal delivery of drugs-loaded MNs were evaluated. Two-layer dissolving MN made of gelatin and carboxymethyl cellulose (CMC) can penetrate the epidermis and enhance the diffusion depth of low and high molecular weight model drugs (rhodamine 6G and insulin-FITC). Ex vivo studies showed that almost 50% of insulin was released after 1 h and the cumulative permeation reached 80% after 5 h. In addition, the in vivo studies showed the relative pharmacologic availability (RPA) and relative bioavailability (RBA) of insulin from gelatin/CMC MN patches were 95.6% and 85.7%, respectively. Moreover, the ex vivo and in vivo studies of MN made of two different molecular weight of polyvinylpyrrolidone (PVP, 10 and 360 kDa) MN, with 1:3 ratio were investigated. Ex vivo studies revealed that this MN can enhance the permeation efficiency of model drugs, lissamine green B and bovine serum albumin-FITC. The in vivo studies showed the RPA of insulin from PVP MN patches was 108%. The RPA and RBA results showed both insulin-loaded MNs have similar efficiency to hypodermic injection in the regulation of blood glucose. Briefly, both studies demonstrated two-layer dissolving MN patches which achieved efficient transdermal delivery of insulin, can be used as an alternative device to treat diabetes.

References

- Agarwal, T., Narayana, S. N., Pal, K., Pramanik, K., Giri, S., and Banerjee, I. (2015). Calcium alginate-carboxymethyl cellulose beads for colon-targeted drug delivery. *Int J Biol Macromol* **75**, 409-17.
- Hultstrom, M., Roxhed, N., and Nordquist, L. (2014). Intradermal insulin delivery: a promising future for diabetes management. *J Diabetes Sci Technol* **8**, 453-7.
- Ito, Y., Hirono, M., Fukushima, K., Sugioka, N., and Takada, K. (2012). Two-layered dissolving microneedles formulated with intermediate-acting insulin. *Int J Pharm* **436**, 387-93.
- Kodaira, H., Tsutsumi, Y., Yoshioka, Y., Kamada, H., Kaneda, Y., Yamamoto, Y., Tsunoda, S., Okamoto, T., Mukai, Y., Shibata, H., Nakagawa, S., and Mayumi, T. (2004). The targeting of anionized polyvinylpyrrolidone to the renal system. *Biomaterials* **25**, 4309-15.
- Lee, I. C., Lin, W. M., Shu, J. C., Tsai, S. W., Chen, C. H., and Tsai, M. T. (2017a). Formulation of two-layer dissolving polymeric microneedle patches for insulin transdermal delivery in diabetic mice. *J Biomed Mater Res A* **105**, 84-93.
- Lee, I. C., Wu, Y.-C., Tsai, S.-W., Chen, C.-H., and Wu, M.-H. (2017b). Fabrication of two-layer dissolving polyvinylpyrrolidone microneedles with different molecular weights for in vivo insulin transdermal delivery. *RSC Advances* **7**, 5067-5075.
- Ling, M. H., and Chen, M. C. (2013). Dissolving polymer microneedle patches for rapid and efficient transdermal delivery of insulin to diabetic rats. *Acta Biomater* **9**, 8952-61.
- Nathan, D. M., Genuth, S., Lachin, J., Cleary, P., Crofford, O., Davis, M., Rand, L., and Siebert, C. (1993). The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* **329**, 977-86.
- Owens, D. R., Zinman, B., and Bolli, G. (2003). Alternative routes of insulin delivery. *Diabet Med* **20**, 886-98.
- Papadimitriou, S. A., Barmapalexis, P., Karavas, E., and Bikiaris, D. N. (2012). Optimizing the ability of PVP/PEG mixtures to be used as appropriate carriers for the preparation of drug solid dispersions by melt mixing technique using artificial neural networks: I. *Eur J Pharm Biopharm* **82**, 175-86.
- Pozzilli, P., Raskin, P., and Parkin, C. G. (2010). Review of clinical trials: update on oral insulin spray formulation. *Diabetes Obes Metab* **12**, 91-6.
- Prausnitz, M. R. (2004). Microneedles for transdermal drug delivery. *Adv Drug Deliv Rev* **56**,

581-7.

Prausnitz, M. R., and Langer, R. (2008). Transdermal drug delivery. *Nat Biotechnol* **26**, 1261-8.

Singh, I., and Morris, A. P. (2011). Performance of transdermal therapeutic systems: Effects of biological factors. *Int J Pharm Investig* **1**, 4-9.

Sullivan, S. P., Koutsonanos, D. G., Del Pilar Martin, M., Lee, J. W., Zarnitsyn, V., Choi, S. O., Murthy, N., Compans, R. W., Skountzou, I., and Prausnitz, M. R. (2010). Dissolving polymer microneedle patches for influenza vaccination. *Nat Med* **16**, 915-20.

Ullm, S., Kruger, A., Tondera, C., Gebauer, T. P., Neffe, A. T., Lendlein, A., Jung, F., and Pietzsch, J. (2014). Biocompatibility and inflammatory response in vitro and in vivo to gelatin-based biomaterials with tailorable elastic properties. *Biomaterials* **35**, 9755-9766.