Non-Fickian Transport of Pioglitazone from a CMC/PVA/SDS Blend Patch Gel

Sharif M. Shaheen*, 1, Nazir Hossen
1Department of Pharmacy, University of Rajshahi, Rajshahi, Bangladesh
2Institute of Polymers, Bulgarian Academy of Sciences, Sofia, Bulgaria.

Correspondence authors: Sharif M. Shaheen, Department of Pharmacy, University of Rajshahi, Rajshahi, Bangladesh and Institute of Polymers, Bulgarian Academy of Sciences, Sofia, Bulgaria.
E-mail: smshaheen2001@yahoo.com

Citation: Sharif M. Shaheen et al. (2015), Non-Fickian Transport of Pioglitazone from a CMC/PVA/SDS Blend Patch Gel. Int J Pharm Sci & Scient Res. 1:1, 46–52. DOI: 10.25141/2471-6782-2015-1.0001

Copyright: ©2015 Sharif M. Shaheen et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited

Received: October 26, 2015; Accepted: November 06, 2015; Published: December 24, 2015

Abstract

Drugs having narrow absorption window in GIT like pioglitazone has poor absorption and needs alternative route to be delivered. In order to introduce transdermal applicability of pioglitazone here we formulated a few preparations of CMC/PVA/SDS blend patch gel containing pioglitazone and evaluated its kinetic feasibility for transdermal delivery in vitro. The kinetic behavior of pioglitazone delivery from the patch gel showed an interesting Non-Fickian Transport, somewhere tends to be Case–II Transport. SDS facilitated the pioglitazone movement through the polymeric macromolecular network, increasing the kinetic constant value in Peppas-Korsmeyer Model of drug delivery. PVA/CMC blend patch gel showed a super Case–II Transport of pioglitazone. All these data suggest that the polymeric blend system of CMC/PVA/SDS patch gel containing pioglitazone could be a potential topical dosage form in respect of transdermal anti-diabetic drug delivery.

Key words: Pioglitazone Delivery, Patch Gel, Non-Fickian Transport, Topical Dosage Form

Introduction

Pioglitazone is the member of the thiazolidinedione family, a novel insulin-sensitizing agent that has been developed for the treatment of insulin resistance, one of the most common abnormalities in type 2 diabetic patients [1]. This agent can improve glucose and, in part, lipid metabolism by increasing insulin sensitivity in insulin-sensitive tissues in diabetic patients [2–5]. Na–CMC is the sodium salt of a polycarboxymethyl ether of cellulose. The BP specifies a sodium content of 6.5 to 10.8% and the USP 6.5 to 9.5%, both calculated on the dry substances. It is a white to cream color, less or almost odorless, hygroscopic powder or granules. It is easily dispersed in water forming colloidal solution; practically insoluble in alcohol, ether and most other organic solvents. The BP species that a 1% solution in water has a pH of 6.0 to 8.0; the USP species a pH range of 6.5 to 8.5. Na–CMC should be biocompatible, non-toxic, non-absorbable, strongly non-covalent adhesive
and Economic [6,7].

The most important goals in adding of Na-CMC consist of drug targeting, controlled and sustained releasing, increasing of residence time, decreasing of adverse effects and minimizing of the first pass effect and long-term drug delivery [2–5].

Polyvinyl alcohol (PVA) is a well-known polymer, which can generate hydrogels by physical or chemical crosslinking [7–13, 34–40]. PVA has been used to develop new materials for different areas such as injectable polymers [14–17], medicine [18]. drug release [19–38], sensors [40], cell encapsulation material [12], etc.

One long–standing approach for improving transdermal drug delivery uses penetration enhancers (also called sorption promoters or accelerants) which penetrate into skin to reversibly decrease the barrier resistance. Numerous compounds have been evaluated for penetration enhancing activity, including sulphoxides (such as dimethylsulphoxide, DMSO), Azone (e.g. laurocapram), pyrrolidones (for example propylene glycol, PG, a common excipient in topically applied dosage forms), surfactants (also common in dosage forms) and terpenes. Sodium dodecyl sulphate (SDS) is a penetration enhancer which intensifies the release of drug from the transdermal drug delivery system patch [41].

A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a time-released dosage dose of medication through the skin for treating systemic illnesses. Since early 1980s, this dosage form of transdermal therapeutic system (TTS) has been available in the pharmaceutical market. Such a system offers a variety of significant clinical benefits over others, such as tablets and injections. For examples, it provides controlled release of the drug into the patient, and enables a steady blood-level profile, leading to reduced systemic side effects and, sometimes, improved efficacy over other dosage forms [41]. In addition, the dosage form of transdermal patches is user-friendly, convenient, painless, and offers multi–day dosing. It is generally accepted that they offer improved patient compliance [42].

In these regards, the transdermal therapeutic system is of particular clinical significance for prevention and long–term treatment of the chronic diseases like diabetes.

Here in order to introduce an efficient patch gel to be designed for a transdermal anti–diabetic dosage form, CMC/PVA/SDS blend gel was prepared and a potential antidiabetic drug release behavior was evaluated.

**Materials and methods:**

**Materials:**

Pioglitazone was graciously donated by Square Pharmaceuticals Ltd. Pabna Plant, Pabna. Carboxy Methyl Cellulose (CMC) and Poly Vinyl Alcohol (PVA) were originated from Fluka, Switzerland, purchased from Jasco, Rajshahi and provided from Pharmaceutics Laboratory, Rajshahi University, Bangladesh. Sodium Lauryl Sulphate (Na–LS) was a potential antidiabetic drug release behavior.

**Methodology:**

**Formulation of CMC-based TDS patch and drug loading:**

TDS–patch were formulated with the help of different polymers (Na–CMC and PVA) and penetration enhancer (Na–LS). First one hundred milligrams of pioglitazone, sodium Lauryl Sulphate and different percentage of polymers were accurately weighed and PVA after keeping in a beaker which contains 8 ml distilled water was heated in a hot plate at 1000c or above. Drug was added in the melted PVA and mingled properly with a glass rod. In the meanwhile, different percentage of carboxy methyl cellulose were loaded in the respective formulations to formulate transdermal drug delivery system patches and placed separately in film boxes. The composition of TDS–patch is given in Table 1.

**Freezing and thawing process:**

The Patches obtained in this way were cooled and introduced separately in respective Film box. Then the film boxes with CMC–based TDS –patches were subjected to three successive freezing (at–20oC) for 16 h followed by thawing for 8 h (at room temperature). In this way three successive cycles were performed to get the perfect cross–linked hydrogel patch with good mechanical resistance, white and opaque, which proves heterogeneous structure [6].

**Preparation of Dissolution medium:**

For the preparation of ethanol in water (50:50) dissolution medium rectified spirit and distilled water were used. 500 ml ethanol and 500 ml of water were measured in a 500 ml volumetric flask respectively and taken in 1000 ml volumetric flask and shaken properly to prepare 1 litre of ethanol–water medium. The volume was adjusted by adding drop wise freshly prepared ethanol–water medium.

**Dissolution rate studies:**

The dissolution studies of pioglitazone in TDS patch gel containing different amount of CMC, PVA and same amount of Na–LS (1%) in separate formulations were carried out in an “Electrolab Tablet Dissolution Tester USP XX TDT–06”. The paddle rotation was set at 50 rpm and temperature was controlled at 32ºC±2ºc using 900 ml dissolution medium. A five milliliter sample was taken at regular interval, which was immediately compensat–ed for the same amount of fresh medium previously heated at 32ºC. All the formulations were studied triplicate.

**Working curve for pioglitazone:**

To prepare a working curve for Pioglitazone in mixture (Ethanol in water, 50:50) various dilute solutions were made and UV light absorption was checked at λ max of 288 nm. Then a standard curve was prepared plotting absorbance data against drug concentration.
The dissolution profile of all the batches was fitted for Zero order, First order, Higuchi model and Korsmeyer-Peppas model to ascertain the kinetic release pattern of pioglitazone. All these information could potentiate pioglitazone delivery from the patch gel in a controlled fashion, which could be a future promising transdermal anti-diabetic dosage form.

**Conclusion:**

PVA/CMC blend patch gel offers pioglitazone a super case-II Transport without SDS. SDS inclusion changed release behavior from super case-II to Non-Fickian Transport with increasing CMC or PVA concentration. These information could potentiate pioglitazone delivery from the patch gel in a controlled fashion, which could be a future promising transdermal anti-diabetic dosage form.

**Acknowledgement:**

The work was supported by the Grant No.2001/714 (2006-2007) awarded by BCSIR (Bangladesh Council of Scientific and Industrial Research). No conflict of interest was declared.

**References**

1. C.A. Hofmann, J.R. Colca, New oral thiazolidinediones: an antidiabetic agent’s act as insulin sensitizers. Diabetes Care 15 (1992), 1075–1078.
2. S.L. Suter, J.J. Nolan, P. Wallace, B. Gumbiner, J.M. Olefsky, Metabolic effects of new oral hypoglycemic agent CS-045 in NIDDM subjects, Diabetes Care 15 (1992), 193–203.
3. V.A. Fonseca, T.R. Valiquett, S.M. Huang, M.N. Ghazzi, R.W. Whitecomb, Troglitazone monotherapy improves glyemic control in patients with type 2 diabetes mellitus: a randomized, controlled study. The Troglitazone Study Group. J. Clin. Endocrinol. Metab. 83 (1998) 3169–3176.
4. S. Aronoff, S. Rosenblatt, S. Braithwaite, J.W. Egan, S. Olefsky, Metabolic effects of new oral hypoglycemic agent CS-045 in NIDDM subjects, Diabetes Care 15 (1992), 1075–1078.
5. G. M. Kipnes, A. Kosnick, M.S. Rendell, J.W. Eagan, A.L. Mathisen, R.L. Schneider, Pioglitazone hydrochloride in combination with sulfonylurea therapy improves glycemic control in patients with type 2 diabetes mellitus: a randomized, placebo-controlled study, Am. J. Med. 111 (2001) 10–17.
6. Silvia Patachia a, Artur J.M. Valente b, Claudia Baciu a. Effect of non-associated electrolyte solutions on the behaviour of poly (vinyl alcohol)—based hydrogels, European Polymer Journal, 43 (2007) 469–487.
7. S. Aronoff, S. Rosenblatt, S. Braithwaite, J.W. Egan, S. Olefsky, Metabolic effects of new oral hypoglycemic agent CS-045 in NIDDM subjects, Diabetes Care 15 (1992) 193–203.
8. S. Aronoff, S. Rosenblatt, S. Braithwaite, J.W. Egan, S. Olefsky, Metabolic effects of new oral hypoglycemic agent CS-045 in NIDDM subjects, Diabetes Care 15 (1992) 193–203.
9. Hassan CM, Peppas NA. Structure and applications of poly(vinyl alcohol) hydrogels produced by conventional crosslinking or by freezing/thawing methods. Adv Polym Sci 2000;153:37–65.
10. Hernandez R, Sarafian A, Lopez D, Mijangos C. Viscoelastic properties of poly(vinyl alcohol) hydrogels and ferrogels obtained through freezing–thawing cycles. Polymer 2004; 46:5543–9.

**Table 2. Kinetic profiles of Pioglitazone release from the patch gels.**

| CMC/PVA Combination | Sample no. | Release Rate (O order, % Release/h) | Diffusion Exponent (n) | Kinetic Constant (x 10^-4 % min^-1) | Corr. Coeff. |
|---------------------|-----------|------------------------------------|-----------------------|--------------------------------------|--------------|
| Sample no-1         | 1         | 1.5                                 | 0.9037                | 4.39                                 | 0.985        |
| Sample no-2         | 2         | 1.6                                 | 0.8548                | 7.29                                 | 0.990        |
| Sample no-3         | 3         | 1.64                                | 0.8543                | 7.98                                 | 0.994        |
| Sample no-4         | 4         | 1.66                                | 0.8275                | 10.51                                | 0.995        |
| Sample no-5         | 5         | 1.67                                | 0.7357                | 22.10                                | 0.991        |
| Sample no-6         | 1.85      | 0.7188                              | 28.00                 | 0.998                                |              |

**Figure 3. Standard curve of pioglitazone.**

**Figure 4. CMC/PVA/SDS Patch gels of pioglitazone.**
11. Hennink WE, van Nostrum CF. Novel crosslinking methods to design hydrogels. Adv Drug Deliv Rev 2002; 54:13–36.
12. Oh HJ, Kim SH, Baek YJ, Seong GH, Lee SH. Hydrodynamic micro-encapsulation of aqueous fluids and cells via ‘on the fly’ photopolymerization. J Micromech Microeng 2006;16:295–301.
13. Lobo VMM, Valente AJM, Polischuk AYa, Geuskens G. Transport of non-asociated electrolytes in acrylamide hydrogels. J Mol Liquids 2001;94:179–92.
14. Fei JQ, Gu LX. PVA/PAA thermo-crosslinking hydrogel fiber: preparation and pH-sensitive properties in electrolyte solution. Eur Polym J 2002;38:1653–63.
15. Szilagyi A, Zrinyi M. Temperature induced phase transition of interpenetrating polymer networks and cells via ‘on the fly’ photopolymerization. J Micromech Microeng 2006;16:295–301.
16. Chun HJ, Lee SB, Nam SY, Ryu SH, Jung SY, Ahn WM. Engineering the tissue which encapsulates cells by using micro-encapsulation: methods, applications and engineering principles. Rev Chem Eng 1996;12:5–205.
17. Chen H, Hsieh YL. Ultrafine hydrogel fibers with poly(acrylic acid) hydrogel. J Ind Eng Chem 2005;11:556–60.
18. Shankaraw A, Kitzman B, Truskey GA, Reichert WM. Engineering the tissue which encapsulates subcutaneous implants. 1. Diffusion properties. J Biomed Mater Res 1997; 37:401–12.
19. Kim SY, Lee YM. Drug release behavior of electroactive polyanionic (poly(vinyl alcohol)/poly(acrylic acid) IPN hydrogels under an electric stimulus. J Appl Polym Sci 1999; 74:1752–61.
20. Seabra AB, de Oliveira MA, Polysaccharides: blending films for local nitric oxide release. Biomaterials 2004;25(17):3773–82.
21. Patil SD, Papadimitrakopoulos F, Burgess DJ. Dexamethasone-loaded poly(lactic-co-glycolic) acid microspheres/poly(vinyl alcohol) hydrogel composite coatings for inflammation control. Diabetes Technology Therapeutics 2004; 6(6):887–97.
22. Mandal TK, Bostanian LA, Graves RA, Chapman SR. Poly(D,L-lactide-co-glycolide) encapsulated poly(vinyl alcohol) hydrogel as a drug delivery system. Pharm Res 2002;19(11):1713–9.
23. Galeska I, Kim T, Patil SD, Bhardwaj U, Chattopadhayay D, Papadimitrakopoulos F, et al. Controlled release of dexamethasone from PLGA microspheres embedded within polyacid-containing PVA hydrogels. AAPS J 2005;07(01):E231–E240. doi:10.1208/aapsj071222.
24. Jagur–Grodzinski J. Biomedical application of functional polymers. React Funct Polym 1999; 39:99–138.
25. Malafaya PB, Silva GA, Baran ET, Reis RL. Drug delivery therapies II. Strategies for delivering bone regenerating factors. Curr Opin Solid State Mater Sci 2002; 6:297–312.
26. Hennink WE, Jong SJ, Bos GW, Veldhuis TFJ, van Nostrum CF. Biodegradable dextran hydrogels crosslinked by stereocomplex formation for the controlled release of pharmaceutical proteins. Int J Pharmaceut 2004; 277:99–104.
27. He L, Buckton G, Gaisford S. Evaluating the interactions and release parameters of various drugs from hydrogels. JPP 2005; 57 (Suppl.).
28. Pearston M, Barrow, Gateley DC, Anstey A, Wilke N, Morrissey A, et al. Hydrogels based on PLGA–PEG–PLGA triblock co-polymers as sustained release drug delivery devices. J Pharm Pharmaceut Sci 2002; 5:431–44.
29. Zhang Y, Jiang M, Zhao J, Zhou J, Chen D. Colloidal devices. AAPS J 2005;07(01):E231–E240. doi:10.1208/aapsj071222.
30. Anseth KS, Metters AT, Bryant SJ, Marten PJ, Elisseeff JH, Bowman CN. In situ forming degradable networks and their application in tissue engineering and drug delivery. J Controlled Release 2002; 78:199–209.