Research Article

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

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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].

Poly vinyl 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 intelligent polymers [14–17], medicine [18], drug release [19–39], 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), Azones (e.g. laurocapram), pyrrolidones (for example 2-pyrrolidone, 2P), alcohols and alkanols (ethanol, or decanol), glycols (for example propylene glycol, PG, a common excipient in topically applied dosage forms), surfactants (also common in dosage forms) and terpenes. Sodium dodecyl sulfate (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 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)

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). Firstly 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 100°C 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.

Figure 1. CMC/PVA Patch gel of pioglitazone

Figure 2. Pioglitazone release studies

Formulation No. (x 3)	Pioglitazone (mg)	Carboxy Methyl Cellulose (CMC) mg	Poly Vinyl Alcohol (PVA) mg	Sodium Lauryl Sulphate (Na-LS) mg	Water (ml)
FM-1	100	1500	400	---	8
FM-2	100	1000	900	---	8
FM-3	100	1900	---	---	8
FM-4	100	1500	300	100	8
FM-5	100	1000	800	100	8
FM-6	100	1800	---	100	8

Table 1. Formulation of CMC-based TDS-patch gel

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. 500ml 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 XXI TDT-06”. The paddle rotation was set at 50 rpm and temperature was controlled at $32^{\circ}\text{C} \pm 2^{\circ}\text{C}$ using 900ml dissolution medium. A five milliliter sample was taken at regular interval, which was immediately compensated for the same amount of fresh medium previously heated to 32°C . 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 269 nm. Then a standard curve was prepared plotting absorbance data against drug concentration

Figure 3. Standard curve of pioglitazone

Figure 4. CMC/PVA/SDS Patch gels of pioglitazone.

Result and Discussion:–

The dissolution profile of all the batches was fitted for Zero order, First order, Higuchi model and korsmeyer–Peppas model to ascertain the kinetic modeling of the drug release. Korsmeyer–Peppas model explains simple relationship which described drug release from a swelling polymeric system [43]. The model is as follows to find out the mechanism of drug release:

$$M_t/M_\infty = kt^n$$

Where M_t is amount of drug release at time t , M_∞ is total amount of drug present in formulation, k is release rate constant depend on geometry of dosage form and n is the diffusion exponent indicating the mechanism of drug release.

$0.45 \leq n \leq 0.5$ indicates Fickian diffusion, $0.45 < n < 0.89$ follows an anomalous non-Fickian Transport, n

$= 0.89$ implies Case II (relaxational) transport and $n > 0.89$ treats as super case II transport.

Pioglitazone release from the patch gel was evaluated as a function of diffusion exponent, kinetic constant as per Peppas–Korsmeyer model. The release pattern was accumulated around 90% for the above equation and exponent as well as kinetic constant values of the various formulation were illustrated in the following Table 2. Interestingly, almost all the formulation showed non-Fickian Transport mechanism from the patch gel. FM-1 showed super Case-II Transport, where SDS was absent. Increasing PVA or CMC concentration made pioglitazone release as Non-Fickian Transport from the patch gel (FM-2, FM-3). Almost all the system followed Non-Fickian Transport except FM-1. SDS inclusion in the system improved the kinetic constant of the macromolecular net-work system inside the patch gel.

CMC/PVA Combination Sample no.	Release Rate (O' order; % Release /h)	Diffusion Exponent (n) for $0.7 \leq M_t/M_\infty \leq 0.9$	Kinetic Constant ($\times 10^{-4} \% \text{ min}^{-n}$) (k)	Corr. Coeff. (r)
1	1.5	0.9037	4.39	0.985
2	1.6	0.8548	7.29	0.990
3	1.64	0.8543	7.98	0.994
4	1.66	0.8275	10.51	0.995
5	1.67	0.7357	22.10	0.991
6	1.85	0.7188	28.00	0.998

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

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. 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.

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