

***In vitro* Transdermal Delivery of Metformin from a HPMC/ PVA Based TDS-patch at Different pH**

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Abstract

In order to evaluate the pHs effect on the transdermal drug delivery, HPMC/PVA based TDS-patch was prepared. *In vitro* transdermal dissolution was performed at 32 °C at different pHs. Comparatively higher release rate was found in case of pH 7.4 than those of others. pHs 5.4 and 8 showed almost the same release pattern. The release fashion was Higuchi type of diffusion controlled release. This result showed that neutral pH would accumulate the maximum drug from such a TDS patch, where the skin pH (around 5.4) does not support such a release. Sustained release of drug from such a patch prefers skin pH rather than neutral pH.

Keywords: Transdermal drug delivery; Higuchi diffusion; Release rate; Metformin.

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1. Introduction

Transdermal drug delivery system has been designed for avoiding the risk and inconvenience of intravenous therapy, bypassing the liver in terms of first pass elimination, usually providing less chance of an overdose or under dose, allowing easy termination and permitting both local and systemic effects.

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 therapeutic system (TTS) has been available in the pharmaceutical market. Such a system offers a variety of significant clinical benefits over

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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 form [1]. 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 [2].

Metformin hydrochloride (a biguanide type of anti-diabetic drug) lowers both basal and post prandial-elevated blood glucose in patients with non-insulin-dependent diabetes mellitus (NIDDM or type-2 diabetes) whose hyperglycemia cannot be satisfactory managed by diet alone. Some high incidence of concomitant GI symptoms, such as abdominal discomfort, nausea and diarrhea may occur during the treatment [3].

In vitro release evaluation of an anti-diabetic drug metformin hydrochloride has been carried out from a chemically cross-linked hydrogel in phosphate buffer (pH 5.4; 7.4; 8.0). In our study we used the hydrogel cross-linked with polyvinyl alcohol (PVA). Most of the chemical cross-linking agents are toxic and sometimes carcinogenic. Whereas physically cross-linked PVA hydrogels are non-toxic, non-carcinogenic, have good biocompatibility and physical properties. PVA is a hydrophilic polymer swell to become an elastic gel upon water penetration. It is a well known polymer, which can generate hydrogels by physical or chemical cross linking [1-2, 4-11]. It has been used to develop new materials for different areas such as cell encapsulation material [12], drug release [13-18], sensor [19], intelligent polymers [20-22], medicine [23], etc.

Transdermal drug delivery system are designed to support the passage of drug substance from the upper surface of the skin into the systemic circulation. Transdermal drug permeability is influenced mainly by three factors: the mobility of the drug in the vehicle, the release of the drug from the vehicle, and drug permeation through skin. The pH of the skin is 5.4. Therefore, different pH (phosphate buffer at pH 5.4, pH 7.4 and pH 8) are used to evaluate the drug release from TDS patch. The test temperature is typically set at 32 °C, reflecting physiological skin conditions (even though the temperature may be higher when skin is covered).

In this regards the transdermal therapeutic system is of particular clinical significance for prevention and long term treatment of the chronic disease like diabetes. Here HPMC based TDS-patches of metformin were prepared and PVA was included to that preparation to elevate the *invitro* dissolution designed for controlled release TDS-patch and the release rate of metformin from this TDS patch at different pH (phosphate buffer at pH 5.4, pH 7.4 and pH 8) was studied.

2. Materials and Methods

2.1. Materials

Metformin HCl was graciously donated by Drug International Ltd., Dhaka, Bangladesh. HPMC and PVA were purchased from Fluka, Switzerland. Potassium dihydrogen

phosphate (KH_2PO_4) and dipotassium hydrogen phosphate (K_2HPO_4) were procured from local market.

2.2. Methodology

2.2.1. Formulation of HPMC-PVA based TDS- patch and drug loading

TDS-patches were formulated with the help of different polymers (HPMC and PVA). For the preparation of HPMC-PVA based TDS-patch, 7.44% of metformin, 4.186% of PVA, 13.95% of HPMC and 74.42% of water were used.

TDS-patch were formulated with the help of different polymers (HPMC and PVA). Firstly metformin HCl (0.8 g) was accurately weighed. PVA was added in 8 mL distilled water in a beaker and heated in a hot plate. Drug was added in the melted PVA and mingled properly with a glass rod. Meanwhile, HPMC (1.5 g) was added in the respective formulations to formulate transdermal drug delivery system patches and placed separately in film boxes [24]. The composition of TDS-patch is given in Table 1.

Table 1. Formulation of HPMC based TDS-patch.

Formulation code (n = 3)	Metformin HCl (g)	HPMC (g)	PVA (g)	Water (mL)
FM-1	0.8	1.5	0.45	8
FM-2	0.8	1.5	0.45	8
FM-3	0.8	1.5	0.45	8

2.2.2. Freezing and thawing process

The patches obtained were cooled and introduced separately in respective film box. Then the film boxes with HPMC-PVA based TDS-patches were subjected to three successive freezing (at $-20\text{ }^\circ\text{C}$) 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 proved heterogeneous structure [4].

2.2.3. Preparation of dissolution medium

For the preparation dissolution medium, phosphate buffer of pHs 5.4, 7.4, and 8 were used. To prepare 1 L of phosphate buffer of pH 5.4, 1.76 g of dipotassium hydrogen phosphate and 13.61 g of potassium dihydrogen phosphate were taken in a 1000 mL volumetric flask and dissolved in 600 mL of distilled water. Finally the volume was made up to the mark with distilled water. The pH was adjusted to 5.4 and confirmed by pH meter.

For the preparation phosphate buffer (1 L) of pH 7.4, 8.0 g potassium chloride, 0.19 g of potassium dihydrogen phosphate and 2.38 g dipotassium hydrogen phosphate were measured and taken in 1000 mL volumetric flask. The volume was adjusted by distilled water and made it 1L. The pH of the buffer was adjusted to 7.4 and checked by pH meter.

For the preparation of 1 L of phosphate buffer of pH 8, some amount of 0.1 M potassium dihydrogen phosphate was taken in a 1000 mL volumetric flask and then 0.1 M dipotassium hydrogen phosphate was added to that solution to produce buffer of pH 8.

2.3. Determination of λ_{max}

λ_{max} varies from solvent to solvent. The UV spectra were taken from 200 nm to 400 nm for dilute solutions of metformin HCl in previously prepared phosphate buffers of pHs 5.4, 7.4 and 8.

2.4. Calibration curve for metformin HCl

To prepare a calibration curve, different concentration of metformin HCl in phosphate buffers of pHs 5.4, 7.4 and 8 were prepared. Absorbance of each solution was measured at λ_{max} of 233 nm. Then standard curve was prepared plotting absorbance against drug concentration.

2.5. Dissolution rate studies

The dissolution studies of metformin HCl in TDS-patch containing same amount of HPMC and PVA in separate formulations were carried out in an "Electro lab Tablet Dissolution Tester USP XXI TDT-06". The paddle rotation was set at 50 rpm and temperature was controlled at 32 ± 2 °C using 900 mL different dissolution medium at different pH. A 5 mL sample was taken at regular interval which was immediately compensated for the same amount of fresh medium previously heated to 32 °C.

3. Result and Discussion

In this study phosphate buffer (pHs 5.4, 7.4 and 8) was used to evaluate the drug release. Figs. 1 and 2 showed the effect of different pHs on metformin release from HPMC/PVA based TDS patch (Higuchi model). When dissolution of HPMC/PVA based TDS patch at pH 7.4 phosphate buffer was carried out, highest release rate and kinetic constant were observed but when dissolution of HPMC/PVA based TDS patch at pH 5.4 and pH 8 were carried out the same release pattern as well as kinetic constant was observed (Table 2). The release pattern was Higuchi type of diffusion controlled release when percent cumulative release time $r = 0.93-0.94$. The highest release rate as well as the highest kinetic constant at neutral pH (pH 7.4) would accumulate the maximum drug from such a TDS patch.

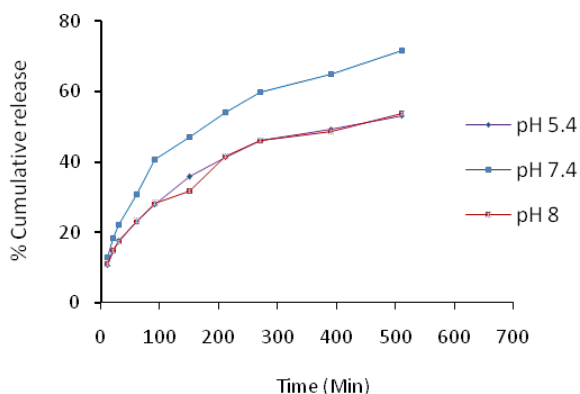


Fig. 1. Effect of different pHs on metformin release from HPMC/ PVA based TDS patch (zero order diffusion model).

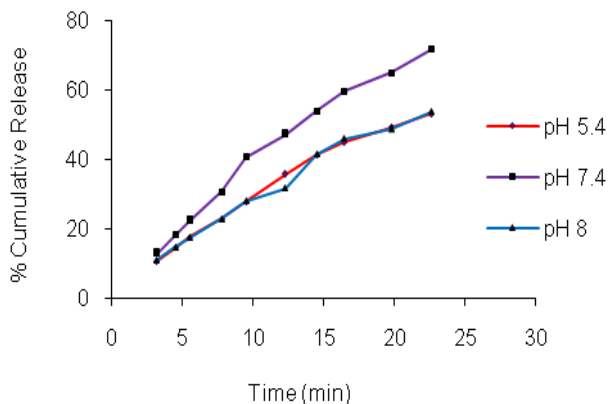


Fig. 2. Effect of different pHs on metformin release from HPMC/PVA based TDS patch (Higuchi model).

Table 2. Kinetic profiles of the effect of pH on metformin release from the HPMC based TDS patch.

pH	Release rate Higuchi model, % release/min ²	Zero order corr. coeff. (r)	Kinetic constant (... × 10 ⁻⁴ % min ⁻ⁿ)	Corr. coeff. (Higuchi model)
pH 5.4	2.846	0.94	4.187	0.99
pH 7.4	3.82	0.93	4.9708	0.988
pH 8	2.90	0.94	4.318	0.99

4. Conclusion

HPMC-PVA based TDS patches of metformin were prepared and their release rate was studied at 32 ± 2 °C (transdermal dissolution temperature) at different pH (phosphate buffer pH 5.4, pH 7.4 and pH 8) the release fashion was Higuchi type of diffusion controlled release. The highest release rate as well as kinetic constant was observed at neutral pH than those of others. The release rate as well as kinetic constant was almost same at pH 5.4 and pH 8. This study predicts that the kinetic profiles of such a TDS patches were influenced with pH and the maximum drug will accumulate at neutral pH where the skin pH does not support such a release. The skin pH permits relatively sustained release of drug from HPMC/PVA based TDS patches of metformin.

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