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IN-VITRO EVALUATION OF TRANSDERMAL PATCHES CONTAINING REMOGLIFLOZIN ETABONATE FOR CONTROLLED DELIVERY

Pharmaceutical Science

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ABSTRACT

Objective: Remogliflozin etabonate (RE) is an orally available prodrug of remogliflozin, a highly selective sodium glucose co-transporter 2 (SGLT2) inhibitor with antihyperglycemic activity use to treat NIDDM (noninsulin-dependent diabetes mellitus). It has an extremely short half life of 2 h and low bioavailability (65%) due to first-pass metabolism which favours the development of transdermal drug delivery system. **Methods:** The present study was focused on formulating and evaluating transdermal patches for controlled delivery of anti-diabetic drug; remogliflozin etabonate (RE). RE loaded matrix type transdermal patches were prepared by solvent casting method using different ratios of HPMC K15M, polyvinylpyrrolidone (PVP), eudragit L100 and carbopol 940. Propylene glycol (PG; 30%) and dimethyl sulfoxide (DMSO; 6%) was used as a plasticizer and penetration enhancer respectively. The prepared patches were evaluated for thickness, folding endurance, weight variation, drug content, scanning electron microscopy (SEM) and in-vitro drug release. **Results:** The thickness of the patches varied from 0.21±0.02 mm to 0.47±0.05 mm. The folding endurance was found to be >150 revealed that the prepared patches were having the capability to withstand the mechanical pressure along with good flexibility. A formulation F7 composed of HPMC K15: carbopol 940 polymer (2:0.25) yielded a lower rate of release after 8 hours (Q8h= 60.35±1.87%) as compared to HPMC K15: PVP polymer and HPMC K15: eudragit L100 polymer due to high viscosity of matrix forming polymer. **Conclusion:** These results suggest that the transdermal patches may be considered as promising carriers for the controlled delivery of remogliflozin etabonate.

KEYWORDS

Transdermal patches, Remogliflozin etabonate, Controlled delivery, Solvent casting method.

INTRODUCTION

Transdermal drug delivery system (TDDS) has been an increased interest in the drug administration via the skin for both local therapeutic effects on diseased skin (topical delivery) as well as for systemic delivery of drugs [1]. The skin as a site of drug delivery has a number of significant advantages over many other routes of drug administration, including the ability to avoid problems of gastric irritation, pH and emptying rate effects, avoid hepatic first-pass metabolism thereby increasing the bioavailability of drug, reduce the risk of systemic side effects The transdermal delivery can also eliminate pulsed entry into the systemic circulation, which might often cause undesirable side effects [2, 3].

Diabetes mellitus is a chronic metabolic disorder characterized by a high blood glucose concentration (hyperglycemia) caused by insulin deficiency, and it is often combined with insulin resistance [4]. The incidence and prevalence of type 2 diabetes mellitus (T2DM) are increasing globally, with about one in 11 adults having diabetes mellitus and 90% of them having T2DM. Remogliflozin etabonate is a pro-drug of remogliflozin [5, 6]. Remogliflozin etabonate (RE) is an orally available prodrug of remogliflozin, a highly selective sodium glucose co-transporter 2 (SGLT2) inhibitor with antihyperglycemic activity use to treat NIDDM (noninsulin-dependent diabetes mellitus). It has an extremely short half life of 2 h and low bioavailability (65%) due to first-pass metabolism. The recommended dosage in T2DM patients is 100 mg administered twice daily; hence, it required frequent dosing [7, 8].

Therefore, the present study aims to prepare transdermal patches containing remogliflozin etabonate to sustain the release and improve bioavailability of drug and patient compliance.

MATERIALS AND METHODS

The remogliflozin etabonate was kindly received as a gift sample by M/s Zydus Cadila Health Care Ltd. (Ahmedabad, India). Polymers were procured from Loba Chemie Pvt. Ltd. (Mumbai, India). Double distilled water was used throughout the study.

Formulation of transdermal patches

In the present study, drug loaded matrix type transdermal patches of RE were prepared by solvent casting method [9] using different ratios of HPMC K15M, polyvinylpyrrolidone (PVP), eudragit L100 and carbopol 940. A weighed amount of polyvinyl alcohol (PVA; 2.5% w/v) was added to a requisite volume of warm distilled water and a homogenous solution was made by constant stirring and intermittent heating at 60°C for a few seconds and poured into glass molds already wrapped with aluminium foil around open ends and were kept for drying at 60°C for 6 h, forming a smooth, uniform, and transparent backing membrane. Backing membrane was used as a support for drug-polymer matrix. The polymers in different ratios as given in Table 1 were dissolved in the solvent system containing water: methanol (1:1). Then, the drug (RE) was added slowly in the polymeric solution and stirred with the help of magnetic stirrer to obtain a uniform solution. Propylene glycol (PG; 30%) was used as a plasticizer. Dimethyl sulfoxide (DMSO; 6%) was used as the penetration enhancer. Then the solution was poured on the glass molds of 5cm×5cm and dried at the room temperature [10].

Table 1: Composition for the formulation of transdermal patches

Polymer	Matrix Forming Polymer	Formulation and Ratio	Drug (mg)	DMSO (%)
HPMC K15M	Eudragit L100	F1 (2: 0.25)	100	6
HPMC K15M	Eudragit L100	F2 (2:0.50)	100	6
HPMC K15M	Eudragit L100	F3 (2:0.75)	100	6
HPMC K15M	PVP	F4 (2: 0.25)	100	6
HPMC K15M	PVP	F5 (2:0.50)	100	6
HPMC K15M	PVP	F6 (2:0.75)	100	6
HPMC K15M	Carbopol 940	F7 (2: 0.25)	100	6
HPMC K15M	Carbopol 940	F8 (2:0.50)	100	6
HPMC K15M	Carbopol 940	F9 (2:0.75)	100	6

Evaluation of transdermal patches

Thickness and folding endurance

The thickness of the prepared transdermal patches was measured by screw gauge with least count at five different sites, and the average was calculated with a standard deviation [11].

The folding endurance of patches was determined by repeatedly folding a strip of film at the same place till it tends to break. It is determined as the number of times the film is folded at the same place either to break the film or to develop visible cracks [11].

Weight variation

The patches were subjected to weight variation by individually weighing ten selected patches randomly and the average was calculated [11].

Drug content uniformity

Each patch from different formulations (patch size of 1 cm^2, equivalent

to 100 mg of drug) was dissolved in phosphate buffer solution (PBS; pH 7.4) and shaken continuously for the 24 h using a magnetic stirrer to extract the drug from the patch. After filtration, % drug content was measured spectrophotometrically at a wavelength of 229 nm [12].

Scanning electron microscopy (SEM) analysis

SEM images of the selected patches were taken at required magnification at room temperature under SEM (LEO 435VP model, Cambridge, UK) for surface appearance [13].

***In-vitro* drug release studies**

In-vitro drug release studies were performed by using a Franz diffusion cell with receptor compartment capacity of 60 ml. The cellulose acetate membrane having a pore size 0.45µ was mounted between the donor and receptor compartment of the diffusion cell. The prepared patches were placed on the membrane and covered with aluminum foil. The receptor compartment of the diffusion cell was filled with PBS pH 7.4. The whole assembly was fixed on a hot plate magnetic stirrer, and the temperature was maintained at 32±0.5^{0}C, because the normal skin temperature of human is 32^{0}C. The samples were withdrawn at different time intervals and analyzed for drug content spectrophotometrically at 229 nm [14].

RESULTS AND DISCUSSION

The prepared formulations with different polymer concentrations were smooth, opaque, flexible and uniform. The thickness of the patches varied from 0.21±0.02 mm to 0.47±0.05 mm. As the solubility decreases and concentration increases would increase the thickness of the patch. Weight variation of all the formulations varied from 0.058±0.010% to 0.107±0.017%. The folding endurance was found to be >150 revealed that the prepared patches were having the capability to withstand the mechanical pressure along with good flexibility. The drug content of all the formulations was in the range of 76.04±0.26% to 95.33±0.09% indicated that the process employed to prepare patches in this study was capable of producing patches with uniform drug content and minimal patch variability (Table 2).

Table 2: Evaluation of transdermal patches

Formulation Code	Thickness (mm)	Folding endurance	Weight variation (%)	Drug content (%)	Q8h (%)
F1	0.23±0.03	281±1.30	0.088±0.012	95.33±0.09	78.81±4.82
F2	0.28±0.01	295±2.32	0.093±0.020	89.71±0.06	73.15±6.32
F3	0.33±0.02	306±2.01	0.107±0.017	76.04±0.26	68.74±0.78
F4	0.36±0.01	217±4.29	0.068±0.010	84.25±0.11	74.04±2.25
F5	0.42±0.04	268±3.18	0.061±0.025	89.70±0.10	75.33±0.89
F6	0.47±0.05	240±2.36	0.064±0.011	82.82±0.08	71.05±0.93
F7	0.21±0.02	161±7.37	0.058±0.020	90.12±0.04	60.35±1.87
F8	0.25±0.01	175±9.79	0.096±0.018	85.84±0.02	63.54±4.42
F9	0.27±0.03	169±9.34	0.100±0.013	82.63±0.09	66.98±3.83

SEM image shows homogeneous and uniform distribution of drugs within the matrix ensuring better activity and drug release (Figure 1).

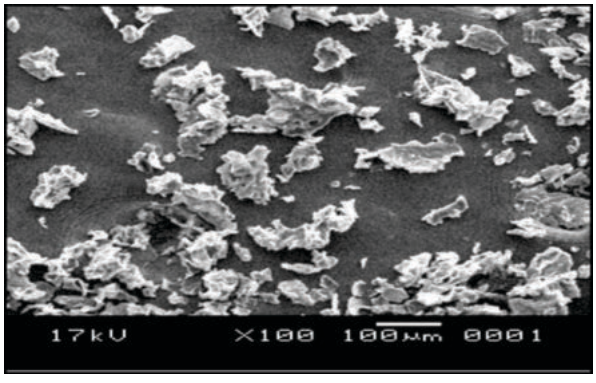

Figure 1: SEM photograph of selected transdermal patch

The order of drug release in PBS of pH 7.4 after 8 hr was found to be F1>F5>F4>F2>F6>F3>F9>F8>F7. It could be concluded that transdermal patches prepared using HPMC K15: Carbopol 940 polymer (2:0.25) yielded a lower rate of release compared to HPMC K15: PVP polymer and HPMC K15: Eudragit L100 polymer. From results, it is obvious that the increase of matrix polymer ratio reduced the efflux of the drug from patches, which is in accordance with its high viscosity. Therefore, the diffusion of RE entrapped in the patches would be expected to occur over a prolonged period of time.

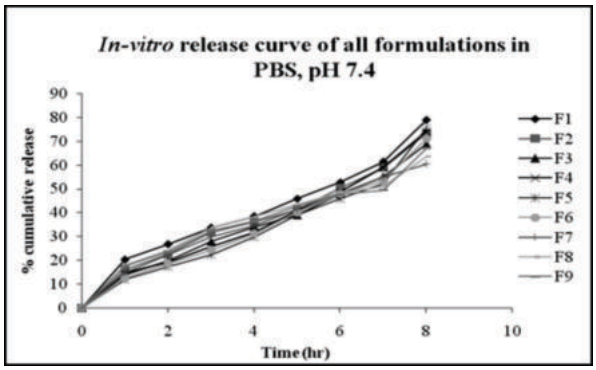

Figure 2: In-vitro release profile of different transdermal patch formulations.

CONCLUSION

A formulation F7 composed of HPMC K15: carbopol 940 polymer (2:0.25) yielded a lower rate of release after 8 hours (Q8h= 60.35±1.87%) as compared to HPMC K15: PVP polymer and HPMC K15: eudragit L100 polymer due to high viscosity of matrix forming polymer. The findings of this study revealed that the problems of remogliflozin etabonate with reported oral formulations for diabetes can be overcome by applying of remogliflozin etabonate topically in the form of a transdermal patch.

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