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Research Article

FORMULATION AND EVALUATION OF VENLAFAXINE HYDROCHLORIDE BUCCAL PATCHES

Adimoolam Senthil*, Chauhan Pratik Navinchandra, Siroya Yakinkumar Ravajibhai, Patel Falguniben Jayantibhai, Vantoor Byruppa Narayanaswamy
Department of Pharmaceutics, Karavali College of Pharmacy, Mangalore-575028, Karnataka, India

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*Dr. A. Senthil, M. Pharm., Ph. D, Professor and HOD, Department of Pharmaceutics, Karavali College of Pharmacy, Mangalore-575028 Karnataka, India.
E mail: senthilac12@gmail.com

ABSTRACT
The present study involves the formulation and evaluation of buccal patches of venlafaxine hydrochloride using sodium alginate with various hydrophilic polymers like carbopol 934 P, carboxymethyl cellulose and hydroxypropylmethylcellulose K4M in various proportions and combinations were fabricated by solvent casting technique. Venlafaxine hydrochloride an antidepressant drug to circumvent the first pass metabolism. Buccal route is excellent for the systemic delivery, there by rendering great bioavailability. A significant reduction in dose and dosing frequency can be achieved, thereby reducing dose dependent side effects, patient compliance and prolonging duration of action. Various physicomechanical parameters like weight variation, thickness, folding endurance, drug content, moisture content, moisture absorption, and various *ex vivo* mucoadhesion parameters like mucoadhesive strength, force of adhesion and bond strength were evaluated. An in vitro drug release study was designed, and it was carried out using commercial semipermeable membrane. All these fabricated patches were sustained for 10 hrs and obeyed first-order release kinetics. Ex vivo drug permeation study was also performed using porcine buccal mucosa, and various drug permeation parameters like flux and lag time were determined

KEYWORDS: Buccal patch, Venlafaxine hydrochloride, Hydroxypropylmethylcellulose K4M, Mucoadhesive.

INTRODUCTION

Buccal delivery of drugs provides an attractive alternate to other conventional methods of systemic drug administration, since buccal mucosa is relatively permeable with rich blood supply and acts as an excellent site for the absorption of drugs[1, 2]. Research had been focused on placing a drug delivery system in a particular region of the body for maximizing biological drug availability and minimizing dose-dependent side effects. The administration of drugs via buccal route facilitates a direct entry of drug molecules into the systemic circulation, avoiding the first pass metabolism and drug degradation in the harsh gastrointestinal environment, which are often associated with oral administration[3–5]. The buccal cavity is easily accessible for self medication, and hence it is safe and well accepted by patients, since buccal patches can be very easily administered and even removed from the application site, terminating the input of drug whenever desired. Moreover, buccal patches provide more flexibility than other drug deliveries.

Venlafaxine hydrochloride is a representative of new class of antidepressants. It acts by inhibiting selectively the uptake of serotonin and noradrenaline but shows no affinity for neurotransmitter receptors[6]. Hence it lacks the adverse anticholinergic, sedative and cardiovascular effects of tricyclic antidepressants. However, the main limitation to therapeutic effectiveness of Venlafaxine hydrochloride is its poor bioavailability (40-45%) and short biological half life (5hrs) necessitating the administration, two or three times daily so as to maintain adequate plasma levels of drug. This necessitates the development of sustained delivery system which permits direct access of the active constituent to the systemic circulation thereby passing first-pass metabolism[7, 8]. During last few decades, mucoadhesive polymers received considerable attention as platforms for buccal delivery of drugs due to their ability to localize the dosage form in the specific regions to enhance drug bioavailability[9]. In previous literature, no attempt has been taken to formulate Venlafaxine hydrochloride buccal patches using sodium alginate along with two other mucoadhesive polymers, CMC and HPMC. CMC and HPMC are both release-retardant polymers. So, they will provide delayed release of drug from buccal patches for long time, if buccal patches are formulated using these polymers. In the present investigation, we made an attempt to formulate Venlafaxine hydrochloride buccal patches using sodium alginate along with various hydrophilic and mucoadhesive polymers like carbopol 934 P, CMC and HPMC in various proportions and combinations to ensure sustained drug release for prolonged periods with satisfactory mucoadhesive properties. The aim of the present investigation was to formulate and evaluate Venlafaxine hydrochloride buccal patches containing mucoadhesive polymeric layer (using sodium alginate, carbopol 934 P, CMC, and HPMC) and drug-free backing membrane composed of PVA-aluminum foil. Aluminum foil was used with adhesive polymer PVA to prevent back release of the drug from the buccal patches.

MATERIALS AND METHODS

Materials

Venlafaxine hydrochloride was gift sample from Lupin pharmaceuticals, Pune, India. Carbopol 934P, Hydroxypropylmethylcellulose, Sodium alginate and Carboxymethylcellulose from Zydus Cadila, India.

Preparation of Venlafaxine hydrochloride buccal patches

A series of buccal patches composed of different proportions and combinations of sodium alginate (600 to 900 mg), HPMC K4M (100 to 300 mg), carbopol 934 P (100 to 300 mg), and CMC (100 to 300 mg) containing Venlafaxine hydrochloride (10 mg) were prepared using a 54-cm^2 petri dish by solvent casting technique. Glycerin was incorporated as a plasticizer at a concentration of 15% w/w of dry weight

of polymers. Backing membrane was casted by pouring 4% w/v aqueous solution of PVA on aluminum foil in petri dishes at 42°C and left for 10 hrs. Phosphate buffer saline, pH 6.8, was used as solvent in the casting method. 10 mg drug was incorporated in mixtures containing different ratios and combinations of polymers and plasticizer. The matrices were prepared by pouring 40 ml of the homogeneous solutions on the PVA-aluminum foil backing membrane. Then, these buccal patches were dried at 42°C in an incubator. After 24 hrs, the dried patches were removed from the petri dishes and kept in desiccators until use. Compositions of formulations were given in Table 1.

EVALUATION OF BUCCAL PATCHES

Weight variation and Thickness

The thickness of the patches was assessed at six different points of the patch using thickness gauze (Mitutoyo, Japan). For each formulation, three randomly selected patches were used. Six films from each batch, as a whole (54 cm^2), were weighed individually and the average weights were calculated.

Folding endurance

The folding endurance was determined manually for the prepared films by repeatedly folding the film at the same place until it broke. The number of times the film could be folded at the same place without breaking or cracking gave the value of folding endurance[10].

Determination of drug content

The drug contents in the buccal patches were determined by dissolving 1 cm^2 patch in 100 ml phosphate buffer saline (pH=6.8) and shaken vigorously for 24 hrs at room temperature. These solutions were filtered through Whatman® filter paper (No. 42). After proper dilution, optical density was measured spectrophotometrically using a UV–VIS spectrophotometer (UV-1700 Double beam spectrophotometer, SHIMADZU Corporation, Japan) at 224 nm against a blank. The experiments were carried out in triplicate.

Moisture content and Moisture absorption

The buccal patches were weighed accurately and kept in desiccators containing anhydrous calcium chloride. After 3 days, the patches were taken out and weighed[11]. The moisture content (%) was determined by calculating moisture loss (%) using the formula:

$$\text{Moisture content (\%)} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

The buccal patches were weighed accurately and placed in the desiccators containing 100 ml of saturated solution of aluminum chloride, which maintains 76% and 86% relative humidity (RH). After 3 days, the films were taken out and weighed. The percentage moisture absorption was calculated using the formula:

$$\text{Moisture absorption (\%)} = \frac{\text{Final weight - Initial weight}}{\text{Initial weight}} \times 100$$

Preparation of porcine buccal mucosa

The porcine buccal mucosa excised from porcine cheek pouch was obtained within 2 hrs of its death from the slaughter house and immediately transported to the laboratory in phosphate buffer solution. The buccal mucosa was separated from the full thickness of the tissue after immersion in distilled water and then in isotonic phosphate buffer, pH 6.8, at 37±1°C for 2 min. The fatty layers were removed by scalpel, and the buccal mucosa was isolated from the underlying tissue. Finally, the mucosa was washed with isotonic phosphate buffer, pH 6.8.

Ex vivo mucoadhesion study

Mucoadhesive strength of all fabricated buccal patches was measured ex vivo (n=3) on a modified physical balance using the method described by Gupta *et al*[12]. A piece of porcine buccal mucosa was tied to the open mouth of a glass vial filled completely with isotonic phosphate buffer, pH 6.8. The glass vial was tightly fitted in the center of a beaker filled with isotonic phosphate buffer (pH 6.8; temperature, 37±1°C). The patches were stuck to the lower side of the rubber stopper with glue. The mass (in gram) required to detach the patches from the mucosal surface gave the measure of mucoadhesive strength (shear stress). The following parameters were calculated from mucoadhesive strength:

$$\text{Force of adhesion (N)} = \frac{\text{Mucoadhesive strength}}{1{,}000} \times 9.81$$

$$\text{Bond strength (Nm}^{-2}\text{)} = \frac{\text{Force of adhesion}}{\text{Surface area}}$$

In vitro release study

The commercially available dialysis membrane was employed for the study[13], and the in vitro drug release study was carried out using a Franz diffusion cell. The effective diffusion area was 1.8 cm^2. The receptor compartment (40 ml) was filled with phosphate buffer saline (PBS), pH 6.8. The patches were applied under occlusion on the dialysis membrane fitted between the donor and receptor compartments of the diffusion cell. The drug release was performed at 37±0.5°C, at a stirring speed of 50 rpm using a magnetic stirrer. Five milliliters of the sample from receptor medium was withdrawn at regular intervals and replaced immediately with an equal volume of phosphate buffer saline, pH 6.8. The amount of drug released into the receptor medium was quantified by using UV–visible spectrophotometer at 224 nm against a blank.

Ex vivo permeability study

The extent and rate of mucosal permeation of drug through the porcine buccal mucosa were carried out using Franz diffusion cell. The effective diffusion area was 1.8 cm^2. The receptor compartment (40 ml) was filled with PBS, pH 6.8, and its temperature was maintained at 37±0.5°C. A 50 rpm stirring speed was applied using a magnetic stirrer to simulate buccal cavity environment. The patch was applied under occlusion on the buccal mucosal surface of the goat fitted between the donor and receptor compartments of the diffusion cell. Five milliliters of the sample from receptor medium was withdrawn at regular intervals and replaced immediately with an equal volume of PBS, pH 6.8. The amount of drug released into the receptor medium was quantified by using UV–visible spectrophotometer at 224 nm.

Drug-Polymer compatibility

Drug-Polymer interaction was observed by IR spectrophotometry. An FTIR study of pure Venlafaxine hydrochloride and physical mixture of Venlafaxine hydrochloride and polymers were performed by KBr dispersion method.

RESULTS AND DISCUSSION

The main aim of the present investigation was to develop and evaluate Venlafaxine hydrochloride buccal patches comprising mucoadhesive polymeric layer using polymers like sodium alginate, CMC, HPMC K4M, and Carbopol 934 P in various combinations with different proportions a drug-free PVA-aluminum foil backing membrane. The physicomechanical evaluation were shown in Table 2 indicates that the weight variation of these formulated buccal patches varied between 2.02 gm (F 5) and 2.12 gm (F 9). The thickness of these patches varied between 0.46 mm (F 2) and 0.59 mm (F 14), the thinnest being formulation F 2 and the thickest being formulation F 14. Folding endurance was measured manually. The highest folding endurance was observed in the case of F 5 (92) and the lowest in the case of F 1 (82). The drug content (%) in all formulations varied between the range 98.33% and 99.64%. This indicates that the drug dispersed uniformly throughout the polymeric film. The moisture content study was done for 3 days. The percentage of moisture content (%) is varied between 0.96% (F 4) and 1.67% (F 3) were shown in Table 2. In most cases, the moisture uptake content was found to increase with increasing concentration of polymers that are more hydrophilic in nature. The low moisture content in the formulation is highly appreciable to protect from microbial contaminations and bulkiness of the patches. Again, low moisture content in formulations helps them to remain stable from being a completely dried and brittle film. The moisture uptake (%) study of various films was done at high relative humidity like 76% for a period of 3 days were shown in Table 2. The moisture uptake by all these formulations was observed at various levels of relative humidity. This moisture uptake (%) by Venlafaxine hydrochloride buccal patches can help to retard any hydrolytic degradation, and patches will remain stable.

In this study, porcine buccal mucosa was used as biological membrane. Various mucoadhesion parameters like mucoadhesive strength, force of adhesion, and bond strength exhibited by these patches was satisfactory for maintaining them in oral cavity were shown in Table 2. Among all these formulated patches, F9 showed maximum mucoadhesive strength (32.38 gm), force of adhesion (0.31N). The in vitro drug release pattern of Venlafaxine hydrochloride from formulated buccal patches is shown in Figure 1, 2. All of these buccal patches slowly released the drug, incorporated and sustained more than 10 hrs. The drug release from buccal patches varied with respect to the polymer composition and nature. An increase in drug release from the buccal patches was found with increasing concentration of polymers that are more hydrophilic in nature. Among all formulations, the maximum in vitro drug release (74.24%) over a period of 10 hrs was observed in the formulation F9. The in vitro drug release was more sustained if the buccal patches composed with high proportion of HPMC K4M. In order to predict and correlate the release behavior of Venlafaxine hydrochloride from different patches, it is necessary to fit into a suitable mathematical model. The in vitro release data from buccal patches were evaluated kinetically using various mathematical models like zero-order, first-order, Higuchi and Koresmeyer–Peppas model equations. The result of curve fitting into these above mentioned mathematical models indicates the drug release behaviors from these formulated buccal patches of Venlafaxine hydrochloride were shown in Table 3. When the release rate of Venlafaxine hydrochloride and their respective correlation coefficients were compared, it was found to follow first-order release kinetics (R2=0.9866 to 0.9984). The ex vivo Venlafaxine hydrochloride permeation from various formulations of buccal patches showed that the drug permeated well across porcine buccal mucosa more than 10 hrs period. There was no interaction between Venlafaxine hydrochloride and polymers.

CONCLUSION

Buccal patches of Venlafaxine hydrochloride using polymers like sodium alginate, CMC, HPMC K4M, and carbopol 934 P in various proportions and combinations showed satisfactory physicomechanical and mucoadhesive characteristics. The proportional amounts of various hydrophilic polymers in various formulations have influence on drug release from these formula Venlafaxine hydrochloride buccal patches. From the present investigation, it can be concluded that such buccal patches of Venlafaxine hydrochloride may provide sustained buccal delivery for prolonged period.

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Table 1: COMPOSITION OF VENLAFAXINE HYDROCHLORIDE BUCCAL PATCHES

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
Venlafaxine HCl (mg)	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Sodium Alginate (mg)	900	800	700	900	800	700	700	600	700	900	800	800	700	600
HPMC K4M (mg)	100	200	300	-	-	-	200	100	100	-	-	-	200	100
Carbopol 934 P (mg)	-	-	-	100	200	300	100	300	200	-	-	100	-	-
Na CMC (mg)	-	-	-	-	-	-	-	-	-	100	200	100	100	300
Glycerine (%)	15	15	15	15	15	15	15	15	15	15	15	15	15	15
Distilled Water (ml)	40	40	40	40	40	40	40	40	40	40	40	40	40	40

Table 2: PHYSICOMECHANICAL AND EX VIVO MUCOADHESIVE EVALUATION OF VENLAFAXINE HYDROCHLORIDE BUCCAL PATCHES

Formulation Code	Weight variation (gm)	Thickness (mm)	Folding endurance	Drug content (%)	Moisture content (%)	Moisture uptake (%) 76%RH	Mucoadhesive Strength (gm)	Force of adhesion (N)
F1	2.12±0.04	0.48	82	98.40	1.32	4.07	25.42	0.25
F2	2.06±0.02	0.46	83	98.51	1.43	4.07	25.62	0.26
F3	2.08±0.06	0.52	80	99.64	1.67	3.17	26.42	0.28
F4	2.03±0.05	0.52	86	99.52	0.96	4.02	28.86	0.26
F5	2.02±0.04	0.48	92	98.57	1.46	3.47	26.08	0.24
F6	2.06±0.05	0.49	86	98.33	1.54	4.64	25.84	0.26
F7	2.04±0.05	0.54	88	98.44	1.26	4.46	26.24	0.28
F8	2.08±0.08	0.52	82	99.46	0.98	4.23	30.26	0.26
F9	2.12±0.09	0.52	86	98.63	1.22	4.17	32.38	0.31
F10	2.10±0.05	0.49	86	98.83	1.62	4.66	20.98	0.24
F11	2.02±0.07	0.52	82	98.98	1.54	4.87	20.86	0.28
F12	2.08±0.08	0.53	84	99.17	1.60	3.86	24.86	0.26
F13	2.04±0.06	0.51	83	99.37	1.46	4.48	23.82	0.32
F14	2.10±0.06	0.59	82	99.37	1.46	4.68	22.86	0.30

Table 3: RESULTS OF CURVE FITTING OF THE *IN VITRO* DRUG RELEASE FROM VENLAFAXINE HYDROCHLORIDE BUCCAL PATCHES

Formulation code	Mathematical models(Kinetics)				
	Zero order	First order	Higuchi	Peppas model	
	r^2	r^2	r^2	n	r^2
F1	0.9766	0.9963	0.7124	1.436	0.9662
F2	0.9898	0.9972	0.6972	1.414	0.9820
F3	0.9768	0.9863	0.7086	1.402	0.9654
F4	0.9654	0.9982	0.6892	1.432	0.9866
F5	0.9712	0.9954	0.7145	1.412	0.9656
F6	0.9702	0.9972	0.7134	1.436	0.9682
F7	0.9756	0.9894	0.6868	1.408	0.9648
F8	0.9826	0.9966	0.7146	1.388	0.9844
F9	0.9839	0.9983	0.7122	1.426	0.9862
F10	0.9646	0.9965	0.6892	1.438	0.9860
F11	0.9742	0.9976	0.6990	1.434	0.9676
F12	0.9678	0.9984	0.6876	1.408	0.9636
F13	0.9633	0.9974	0.6953	1.424	0.9655
F14	0.9679	0.9969	0.6999	1.443	0.9942

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