Development and characterization of mucoadhesive patches for buccal delivery of pregabalin

Abstract:
Pregabalin is a structural analogue of the inhibitory neurotransmitter γ-amino butyric acid (GABA) having short half-life (5-6 hrs) and is used in the management of epilepsy. The aim of this study was to prepare a buccal patch containing Pregabalin by the means of solvent casting method. Six formulations were prepared using different ratio of polymers including HPMC K4M, Eudragit RL, and PVP K30. Since buccal mucosa is relatively permeable with rich blood supply and acts as an excellent site for the absorption of drugs so, it is an attractive alternate to other conventional methods of systemic drug administration. Franz diffusion cell with commercially available dialysis membrane was used for the in-vitro diffusion study of buccal patches for duration of 12 hrs. Kinetics and mechanism of drug release from all formulation was evaluated on the basis of zero order, first order, Hixon-Crowell, Higuchi equation and Peppas model. Based on different parameters i.e. folding endurance, drug content, moisture absorption, moisture loss, water vapor transmission rate in-vitro release study buccal patches of batch F4 (HPMC K4M & Eudragit RL 100) was found to an optimum formulation.
Keywords: Pregabalin, Buccal patch, epilepsy, buccal mucosa, the in-vitro diffusion study.

Introduction:

Buccal delivery refers to a topical route of administration by whichdrugs held or applied in the buccal area, diffuse through the oral mucosa and enter directly into the systemic circulation. Dosage form retained at the site of action by intimate contact[1]. The buccal mucosa has rich blood supply, easy accessibility and is relativelypermeable and provides affluent blood supply, better bioavailability by avoiding first pass metabolism of drugs and a more rapid onset of action. Bioadhesion is a phenomenon of interfacial molecular attractive forces in which two materials, one of which is natural in origin, are held mutually for extensive periods of time by means of interfacial forces for a longer duration[2]. Mucoadhesion is commonly defined as the adhesion between two materials, at least one of which is a mucosal surface. Buccal drug delivery is well accepted by patients because of possibility of self-medication i.e. comfortable application and rapidly termination of dosage form whenever needed[3].

Pregabalin is a structural analogue of the inhibitory neurotransmitter γ-amino butyric acid (GABA)[4]. It is an oral antiepileptic drug used in the management of epilepsy. Pregabalin has been studied for treatment of different disorders, includingmonotherapy in refractory partial seizures, diabetic neuropathy, surgical dental pain and other pain syndromes, postherpetic neuralgia, and social anxiety disorders[5,6].

All these properties make it an ideal candidate to develop a novel dosage form. Keeping these factors, in present study bioadhesive patches of Pregabalin were developed and evaluated in order to provide a controlled and predictable release, to avoid frequentadministration and thus to increase patient compliance.

MATERIALS AND METHODS:

Pregabalin was received from Swiss Pharma Nigeria. HPMC K4M, and PVP K30 was obtained from Divinne Construction and Concrete Expressions Limited, Lagos, Nigeria and Eudragit RL from JuNeng Nigeria Limited, Nigeria. All other chemicals were arrangedfrom Barata Pharmaceuticals, Rivers State Nigeria.

Preparation of mucoadhesive patches

The mucoadhesive films were prepared by solvent casting method. Polymeric solution of different polymers i.e. HPMC K4M, Eudragit RL & PVP K30 was prepared by taking them in different ratio (table-1) by means of distilled water under occasional stirring for 4 hrs. The resulting viscous solution was filtered through nylon gauze to remove debris and suspended particles. Propylene glycol was added as permeation enhancer by constant stirring.The resultant solution was left overnight at room temperature to ensure a clear, bubble-free solution. The solution was poured into a glass petri dish. It was kept for drying to form films. Dried films were slowly removed from the petri plateand cut into appropriate size. Prepared film stored in a desiccator[7].

Table-1: Compositions of the Pregabalin buccal films

S.N.	Ingredients	F1	F2	F3	F4	F5	F6
1.	Pregabalin (mg)	50	50	50	50	50	50
2.	HPMC K4M(mg)	100	-	150	200	-	-
3.	Eudragit RL 100(mg)	-	100	-	150	-	200
4.	PVP K30	100	150	-	-	-	200
5.	Propylene glycol (ml)	2.5	2.5	2.5	2.5	200	-

Characterization and evaluation of Mucoadhesive film

1. Measurement of weight variation and thickness:

The thickness of the Pregabalin buccal patches was assessed at six different points of the patch using thickness gauze (Mitutoyo, Japan). For each formulation, three randomlyselected patches were used and the average weights were calculated[8].

2. Measurement of Folding Endurance:

Folding endurance of Pregabalin buccal patches determined by repeatedly folding one film at the same place up to 200 times till it broke or folded, which is consideredsatisfactory to reveal good patch properties[9].

3. Content Uniformity:

To determine content uniformity, Pregabalin buccal patches were taken at different locations of the prepared film and these films were dissolved in 100mL of pH 6.8 phosphatebuffer solution. The solution was centrifuged at 3000 rpm for 15 min. The supernatant was taken and absorbance was noted spectrophotometrically at 276 nm[10].

4. Moisture content:

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

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

4. Percentage Moisture Absorption (PMA):

The percentage moisture absorption study of Pregabalinbuccal patches was carried out to check the physical stability of the buccal films at high humid conditions. Three 1cm diameter films were cut out and weighed accurately. The films were placed in desiccator containing saturated solution of aluminium chloride, keeping the humidity inside the desiccator at 79.5 %. After 3 days the films were removed, weighed and percentagemoisture absorption was calculated[12].

5. Water Vapour Transmission Rate (WVTR)

WVTR is defined as the quantity of moisture transmittedthrough unit area of film in unit time. A glass bottle was used in the study having length 5cm, with internal diameter of 0.8cm was filled with 2g anhydrous calcium chloride and an adhesive spread across its rim. The Pregabalin buccal patch was fixed over the adhesive and the assembly was placed in constant humidity chamber, prepared using saturated solution of ammonium chloride and maintained at 37 ± 2^0C. The difference in weight after three days was calculated. The vapor transmission rate was obtained as follow[13].

VTR= (Amount of moisture transmitted)/(Area × Time)

7. Percent drug content:

Drug content uniformity was determined by dissolving the Pregabalin buccal patch (10 mm in diameter) from each batch by homogenization in 100 ml of an isotonic phosphate buffer (pH 6.8) for 6 h under occasional shaking. The 5ml solution was taken and diluted with isotonic phosphate buffer pH 6.8 up to 20 ml, and the resulting solution was filtered through a 0.45 mm What man filter paper. Drug content was thendetermined after proper dilution at 276 nm using an UV spectrophotometer[14].

8. **Surface pH:**

Pregabalin buccal patches were left to swell for 1 hour on the surface of the agar plate, the agar plate prepared by dissolving 2% (w/v) agar in warmed isotonic phosphate buffer of pH 6.6 under stirring and the solution was poured into the petri dish, itwas allowed to stand until it solidified to form a gel at room temperature. The surface pH was measured by means of pH paper placed on the surface of the swollen patch[15].

9. In-vitro diffusion study:

Franz diffusion cell with commercially available dialysis membranewas used for the *in-vitro* diffusion study of Pregabalin buccal patches for duration of 12 hrs. The receptor compartment was filled with phosphate buffer saline, 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.The amount of drug released into the receptor medium was measured by means of UV visible spectrophotometer at 276 nm[16].

Table-2: Properties of Pregabalin buccal patches

Code	Thickness (mm)	Weight (mg)	Folding endurance	% Drug content	% Moisture absorption	% Moisture loss	WVTR ($gcm^{-2}h^{-1}$)	Surface pH
F1	0.48±0.25	0.31±0.35	211±1.2	97.41±0.09	12.5±0.48	4.3±0.25	0.358±0.09	6.8
F2	0.49±0.17	0.38±0.09	232±0.8	96.53±0.11	11.31±0.32	3.8±0.41	0.423±0.13	6.9
F3	0.52±0.09	0.37±0.07	225±0.5	95.42±0.53	13.27±0.28	5.2±0.09	0.485±0.21	7.0
F4	0.57±0.08	0.28±0.31	244±0.4	98.32±0.25	9.72±0.15	3.7±0.13	0.511±0.35	7.2
F5	0.51±0.14	0.25±0.42	243±0.9	91.61±0.58	11.44±0.08	3.6±0.27	0.478±0.44	6.7
F6	0.49±0.23	0.32±0.51	246±1.4	94.53±0.42	15.38±0.26	4.9±0.32	0.468±0.53	7.1

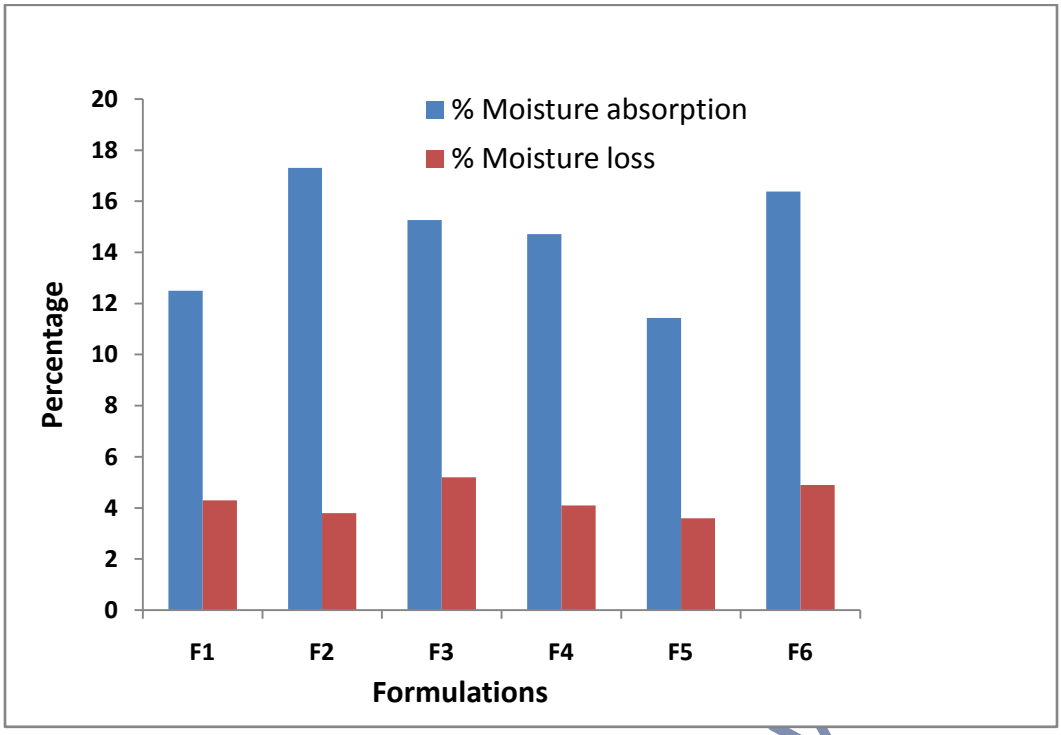

Figure 1: Percentage moisture absorption and moisture loss

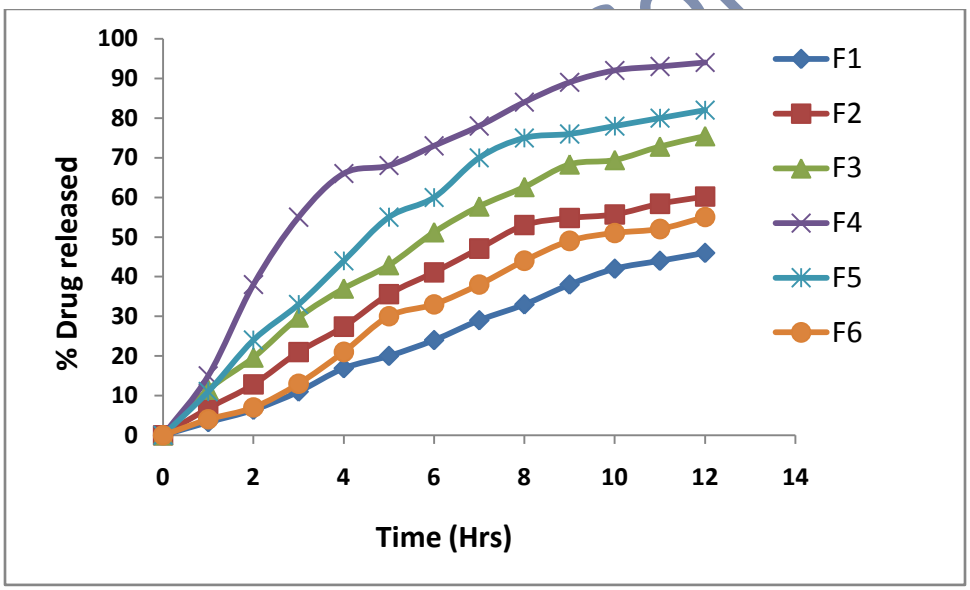

Figure 2: In-vitro diffusion profile of Pregabalin buccal patches

Table 3: Statistical analysis of Pregabalin buccal patches

Code	Zero order	First order	Hixon-Crowell	Higuchi Plot	Korsmeyer- Peppas	
	R	R		R	R	n
F1	0.9865	0.7529	0.8325	0.4058	0.9264	1.0231
F2	0.9547	0.7138	0.8764	0.5037	0.9378	1.1682
F3	0.8871	0.7262	0.8537	0.4485	0.9152	1.0381
F4	0.8358	0.7453	0.7928	0.5132	0.8936	0.9934
F5	0.8549	0.6938	0.7732	0.6028	0.9015	1.1573
F6	0.8932	0.7621	0.8014	0.7325	0.8632	1.1821

Results and discussion:

Pregabalin buccal patches in polymers were prepared by solvent casting method. Formulated patches were subjected to the preliminary evaluation tests. Patches with any imperfections or differing in thickness, weight (or) contentuniformity were excluded from further studies.

The thickness (table 4) of formulated patches varied from 0.48±0.25 to 0.52±0.09 mm. Group F4 (Eudragit RL 100) have highest thickness while group (F1 HPMC K4M and PVP K30) has shown least among all formulations.

The average weight of patch from each batch ranges from 0.25±0.42 to 0.38±0.09 (table- 1). Results indicate that formulations of batch F5 (HPMC K4M) have the least and of batch F4 have the highest mass among the different formulations.

The drug content of films was quite uniform. The average drug content of the films was found to be within the range of 91.61– 98.32 % and the low values of standard deviation and coefficient of variation indicate uniform distribution of the drug withinthe prepared films.

The moisture absorption study of patches was done at a relative humidity of 79.5 % for a period of three days. The low moisture uptake by all the formulations was observed. The low moisture uptake by all the buccal patches can help to retard any hydrolytic degradation, and patches will remain stable. Maximum % moisture loss was shown by formulations of batch F3 (5.2±0.09 %).

Formulation F4 consisting of Eudragit RL 100 has shown highest water vapor transmission rate (0.511±0.35 $gcm^{-2}h^{-1}$).

Surface pH of patches was ranges from 6.7 to 7.2 were found around neutral pH neutral pH and indicates its compatibility with buccal pH. Films did not show any cracks even after folding for more than 200 for all batches. The results indicate that an increase inpolymer concentration increased the folding endurance.

Percentage drug release for the formulations F1, F2, F3, F4, F5 and F6 was found to be 45.32, 61.2, 76.43, 93.76, 82.48 and 55.62 % respectively in a study of 12 hrs (figure 2). It was observed that drug release rate increased by increasing the ratio of HPMC respectively.

The in vitro release data was applied to various kinetic models to predict the drug release kinetic mechanism. Kinetics and mechanism of drug release from all formulation was evaluated on the basis of zero order, first order, Hixon-Crowell, Higuchi equation and Peppas model. Mechanism of drug release pattern i.e.diffusion and swelling was confirmed by Higuchi plots. The Higuchi plots represent of cumulative percentage drug release versussquare root of time. It was concluded that the release of drug from the patches followed the diffusion controlled.

Conclusion:

Nowadays, many researchers are working for the progress of the innovative approach of delivery of drug to improve the safety, effectiveness and patient compliance. The buccal mucosa has a rich blood supply and easily accessible, and suitable for the application of a dosage form to the required site. The aim of the present study was to develop a novel unit dosage form of Pregabalin. A satisfactory attempt was made to developmucoadhesive buccal patches of Pregabalin with different ratio of polymers including HPMC K4M, Eudragit RL, and PVP K30 by solvent casting method. Based on different parameters i.e. folding endurance, drug content, moisture absorption, moisture loss, water vapor transmission rate in-vitro release study buccal patches of batch F4 were found to an optimum formulation.

Conflict of interest:

The author has declared that there is no conflict of interest related to this paper.

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