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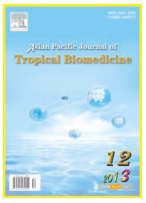

Document heading doi:10.1016/S2221-1691(13)60192-6

Formulation of unidirectional release buccal patches of carbamazepine and study of permeation through porcine buccal mucosa

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PEER REVIEW

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Comments

This is a good study about trans buccal administrations of carbamazepine. This study concentrated on various parameters like mucoadhesion time, mucoadhesive strength, *ex vivo* permeation through porcine mucosa and stability studies under human saliva. This covered almost all important parameters to be considered to understand the drug release mechanism from the formulation.
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ABSTRACT

Objective: To achieve transbuccal release of carbamazepine by loading in unidirectional release mucoadhesive buccal patches.

Methods: Buccal patches of carbamazepine with unidirectional drug release were prepared using hydroxypropyl methyl cellulose, polyvinyl alcohol, polyvinyl pyrrolidone and ethyl cellulose by solvent casting method. Water impermeable backing layer (Pidilite® Biaxially-oriented polypropylene film) of patches provided unidirectional drug release. They were evaluated for thickness, mass uniformity, surface pH and folding endurance. Six formulations FA2, FA8, FA10, FB1, FB14 and FB16 (folding endurance above 250) were evaluated further for swelling studies, *ex vivo* mucoadhesive strength, *ex vivo* mucoadhesion time, *in vitro* drug release, *ex vivo* permeation, accelerated stability studies and FTIR and XRD spectral studies.

Results: The *ex vivo* mucoadhesion time of patches ranged between 109 min (FA10) to 126 min (FB14). The *ex vivo* mucoadhesive force was in the range of 0.278 to 0.479 kg/m/s. The *in vitro* drug release studies revealed that formulation FA8 released 84% and FB16 released 99.01% of drug in 140 min.

Conclusions: The prepared unidirectional buccal patches of carbamazepine provided a maximum drug release within specified mucoadhesion period and it indicates a potential alternative drug delivery system for systemic delivery of carbamazepine.

KEYWORDS

Buccal patches, Carbamazepine, Mucoadhesion, Biaxially-oriented polypropylene films, Porcine buccal mucosa

1. Introduction

Epilepsy is a chronic disorder of the brain that affects people of all ages. Around 50 million people worldwide have epilepsy. Carbamazepine is a dibenzazepine derivative mainly used for the treatment of epilepsy, trigeminal neuralgia and bipolar disorder. Carbamazepine and its active metabolite are responsible for adverse drug reactions like dizziness, diplopia, nausea, headache and light-headedness especially at the beginning of treatment and at higher doses[1]. Buccal delivery of drug is an alternate to the conventional method of drug administration, to overcome problems such as high hepatic first pass metabolism and associated adverse drug reactions[2]. Direct access to the systemic circulation through the internal jugular vein bypasses drugs from the hepatic

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Foundation Project: This Research project was supported by RR college of Pharmacy affiliated to Rajiv Gandhi University of Health Sciences, Bangalore, India (Grant No. RRCP\PCEUTICS\IHR&D\231).

Article history:
Received 7 Aug 2013
Received in revised form 16 Aug, 2nd revised form 22 Aug, 3rd revised form 3 Sep 2013
Accepted 19 Nov 2013
Available online 28 Dec 2013

first pass metabolism leads to high bioavailability. The buccal route could be an alternative choice for seizure control in epileptic unconscious patients[3,4]. It is a safer method of drug administration since drug absorption can be easily terminated in case of toxicity by removing the dosage form from the buccal cavity. Considering the low patient compliance of rectal, vaginal, sublingual and nasal drug delivery for controlled release, the buccal mucosa has rich blood supply and its relatively permeable and rapid onset of action can be achieved. As it is confirmed by literature review buccal patches of carbamazepine were not yet formulated and reported. In this present research, mucoadhesive buccal patches were designed to formulate using various combinations of hydrophilic and lipophilic polymers[5].

2. Materials and methods

2.1. Materials

The drug, carbamazepine was obtained as a gift sample from Caplin Point Pharma Ltd, Puducherry, India. The polymers hydroxypropyl methyl cellulose (HPMC-K15M), polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP K-30) and ethyl cellulose (EC) were procured from Sigma-Aldrich, Bangalore. Propylene glycol (PG) and Polyethylene glycol-400 (PEG-400) were purchased from SD Fine Chem Ltd, Bangalore, India. Biaxially-oriented polypropylene film was supplied by Pidilite®, India. All other reagents used were of analytical grade.

2.2. Methods

2.2.1. Preparation of mucoadhesive buccal patches of carbamazepine

Buccal patches of carbamazepine containing different proportions of HPMC K-15M, PVA, PVP K-30 and EC were prepared by solvent casting method[6]. About 2% w/v solutions of HPMC K-15M and PVA were prepared separately using deionized water and stirred for 24 h. The 1% w/v solution of PVP K-30 and EC were prepared in water and ethanol respectively. Two different polymer combinations of HPMC/PVA/PVP and HPMC/PVA/EC were formulated (Table 1). A 32 full factorial design (IBM® SPSS Statistics Version 20) was used to design the experiments for each polymer combination. The total volume of polymer solution used was maintained constant as 30 mL excluding the plasticizer and drug solution. To the above polymeric solutions 2 mL of either PG or PEG-400 was added as plasticizer. To this mixture, 5 mL of ethanolic solution of carbamazepine corresponding to 20 mg per patch (3 cm diameter) was added and mixed thoroughly. Then the above mixture was homogenized for 2 h and then casted on a specially fabricated teflon coated Petri dish (9 cm diameter) by placing on a leveled surface. Inverted funnel was kept over the Petri dish to avoid sudden evaporation. Patches were then allowed to dry at room temperature for 2 h and further dried in a hot air oven at 40 °C for 48 h. The dried patches were carefully examined for imperfections or entrapped air bubbles and cut into 3 cm diameter patches equivalent to 20 mg of carbamazepine. The patches were affixed on one side with a water impermeable backing layer (Pidilite® Biaxially-oriented polypropylene film) to provide unidirectional drug release and packed in an aluminium foil to store in a desiccator at room temperature for further studies[7].

2.2.2. Evaluation of patches

2.2.2.1. Mass uniformity, thickness, folding endurance

Mass uniformity and thickness of prepared buccal patches (without backing layer) were measured using a digital balance and a digital vernier caliper respectively. Folding endurance of the patches (without backing layer) were determined by repeatedly folding a patch at the same place till it broke or develop visible cracks or folding above 250 times without breaking.

2.2.2.2. Surface pH

Surface pH of the buccal patches (without backing layer) were determined by a modified method reported by Bottenberg *et al*[8], An agar plate was prepared by dissolving 2% (w/v) agar in warmed simulated saliva (pH 6.2) and allowed to solidify at room temperature. Buccal patches were placed and allowed to swell for 2 h on the surface of an agar plate. The surface pH was measured by bringing a combined glass electrode in contact with the surface of the swollen patch, allowing it to equilibrate for 1 min. The experiment was repeated thrice and the averages were taken.

2.2.2.3. Drug content uniformity

For drug content uniformity, a 3 cm patch (without backing membrane) was separately dissolved in 100 mL of ethanol and simulated saliva solution (pH 6.2) mixture (20:80) for 12 h under occasional shaking. The resultant solution was filtered by 0.45 μm filter and the content of carbamazepine was estimated spectrophotometrically at 285 nm (Shimadzu 1800, Japan). The averages of three determinations were taken.

2.2.2.4. Swelling study

The initial weight of the patch (without backing membrane) was determined using a digital balance (W_0). Then the patches were allowed to swell on the surface of an agar plate (described under measurement of surface pH) and kept in an incubator maintained at 37 °C. Weight of the swollen patch was determined (W_t) at predetermined time intervals for 120 min. The percentage of swelling (% S) was calculated using the following equation[9]:

$$\% S = \frac{W_t - W_o}{W_o} \times 100$$

Where W_t is the weight of swollen patch after time t, W_0 is the initial weight of patch at t=0.

2.2.2.5. Ex vivo mucoadhesion time

The *ex vivo* mucoadhesion (residence) time was determined

Table 1
Composition of mucoadhesive buccal patches of carbamazepine.

Formulations		Carbamazepine (mg)	Polymersa			
Plasticizer PG (2 mL)	Plasticizer PEG-400 (2 mL)		HPMC K15M (2%, w/v) (mL)	PVA (2%, w/v) (mL)	EC (1%, w/v) (mL)	PVP K30 (1%, w/v) (mL)
FA1	FB1	20	10.0	10.0	10.0	
FA2	FB2	20	12.0	12.0	6.0	
FA3	FB3	20	13.3	13.3	3.3	
FA4	FB4	20	12.0	6.0	12.0	
FA5	FB5	20	15.0	7.5	7.5	
FA6	FB6	20	17.2	8.6	4.3	
FA7	FB7	20	13.3	3.3	13.3	
FA8	FB8	20	17.2	4.3	8.6	
FA9	FB9	20	20.0	5.0	5.0	
FA10	FB10	20	10.0	10.0		10.0
FA11	FB11	20	12.0	12.0		6.0
FA12	FB12	20	13.3	13.3		3.3
FA13	FB13	20	12.0	6.0		12.0
FA14	FB14	20	15.0	7.5		7.5
FA15	FB15	20	17.2	8.6		4.3
FA16	FB16	20	13.3	3.3		13.3
FA17	FB17	20	17.2	4.3		8.6
FA18	FB18	20	20.0	5.0		5.0

Total volume of polymer solution used in each formulation was 30 mL.

by locally modified USP disintegration apparatus using 800 mL of simulated saliva (pH 6.2) and the temperature was maintained at (37±1) °C. A porcine buccal mucosa obtained from local slaughter house within 2 h of slaughter was used to mimic the human buccal mucosa in the *in vivo* conditions. The mucosal membrane was carefully separated by removing the underlying connective tissues using surgical scissors. The separated mucosal membrane was washed with deionized water and then with simulated saliva (pH 6.2)[10]. Porcine buccal mucosa (3 cm diameter) was glued on the surface of a glass slab. One side of the buccal patch was hydrated with one drop of simulated saliva (pH 6.2) and brought into contact with porcine buccal mucosa by gentle pressing with a fingertip for few seconds. The glass slab was vertically fixed to the shaft of the disintegration apparatus and allowed to move up and down (25 cycles per min). The patch was completely immersed in simulated saliva at the lowest point and was out of the solution at the highest point. The time of complete erosion or detachment of the patch from the mucosal surface was recorded as *ex vivo* mucoadhesion time[11].

2.2.2.6. Ex vivo mucoadhesive strength

The force required to detach the attachment of mucoadhesive film from the mucosal surface was applied as a measure of the mucoadhesive strength. This study was carried out on a specially fabricated physical balance assembly. Porcine buccal mucosa was glued on a dry Petri dish surface by placing the mucosal surface outward and it was moistened with few drops of simulated saliva (pH 6.2). The right side pan of the balance was replaced by a glass disc glued with a buccal patch of 3 cm diameter. The balance was adjusted for equal oscillation by keeping sufficient weight on the left pan. A weight of 5 g (w_1) was removed from the left pan, which lowered the pan and buccal patch was brought in contact with pre moistened mucosa for 5 min. Then weights were increased gently on the left pan until the attachment breaks (w_2). The difference in weight (w_2-w_1) was taken as mucoadhesive strength[11]. The mucoadhesive force was calculated from the following equation:

$$\text{Mucoadhesive force (kg/m/s)} = \frac{\text{Mucoadhesive strength(g)}}{1000} \times \text{acceleration due to gravity}$$

Here, acceleration due to gravity 9.8 m/s^{-1}

2.2.2.7. In vitro release study

The *in vitro* drug release study was carried out by using USP XXIII Type-2 rotating paddle dissolution test apparatus (Electrolab, EDT-08Lx). A total of 100 mL of ethanol and simulated saliva solution (pH 6.2) mixture (20:80) was used as dissolution medium at (37±1) °C, and stirred at 50 r/min[12]. A 3 cm diameter buccal patch was fixed on the glass disc with the help of cyanoacrylate adhesive. The disc was put into the bottom of the dissolution vessel, so that the patch remained on the upper side of the disc. Samples (2 mL) were withdrawn at half an hour intervals and replaced with an equal volume of dissolution medium. The samples were filtered through 0.45 μm membrane filter and analyzed spectrophotometrically at 285 nm. The mechanism of drug release from the buccal patches was determined by finding the best fit of the release data to Higuchi, Korsmeyer-Peppas, zero order and first order plots[13].

2.2.2.8. Ex vivo permeation study

The *ex vivo* buccal permeation of carbamazepine through the porcine buccal mucosa was performed using a modified Franz glass diffusion cell. Porcine buccal mucosa was obtained from a local slaughterhouse and used within 2 h

of slaughter. Freshly obtained porcine buccal mucosa was mounted between the donor and receptor compartments. The patch was placed on the smooth surface of mucosa by gentle pressing and the compartments were clamped together. The donor compartment was moistened with 1 mL of simulated saliva (pH 6.2) and the receptor compartment was filled to touch the membrane with a mixture of 100 mL of ethanol and isotonic phosphate buffer (pH 7.4) (20:80). Ethanol was added to prevent saturation of carbamazepine in aqueous medium of receptor compartment [14,15]. The fluid motion in the receptor compartment was maintained by stirring with a magnetic bead at 50 r/min. The temperature was maintained at (37±0.2) °C by water jacket surrounding the chamber. At predetermined time intervals, a 2 mL sample was withdrawn (replaced with fresh medium) and analyzed spectrophotometrically at 285 nm. The permeation study was performed in triplicate.

2.2.2.9. Histopathology study

The effect of ethanolic phosphate buffer (pH 7.4) (20:80 mixture) on permeation behaviour of porcine buccal mucosa which was used in *ex vivo* permeation study was assessed by histopathological examination of mucous membrane. Cross section of formalin preserved and wax mounted tissue specimens were examined under optical microscope[16].

2.2.2.10. Accelerated stability studies

Selected formulations were subjected to accelerated stability testing by placing in glass Petri dishes wrapped with aluminum foil and kept in a stability chamber maintained at (37±0.5) °C and 75%±5% relative humidity for 6 months. Drug content, surface pH, mucoadhesion time and changes in the appearance of all the formulations were evaluated after 1, 2, 3, 4, and 6 months.

2.2.2.11. Stability in human saliva

The stability study of selected buccal patches was performed in natural human collected from normal healthy individuals aged between 25-32 years. Samples were placed in separate Petri dishes each containing 5 mL of human saliva and placed in a temperature controlled oven at (37±0.5) °C for 6 h. Samples were physically examined for changes in shape, colour and texture[3].

2.2.2.12. FTIR spectra and XRD studies

FTIR spectra of selected carbamazepine buccal patches [stored at (40±2) °C/75%±5% relative humidity for 2 months] were recorded. The samples were prepared by potassium bromide disc method and scanned for absorbance spectrum. And the samples of same formulations were subjected to XRD studies. The Powder X-ray diffraction patterns were studied (Anton Paar, TTK 450 diffractometer, Austria) to know the physical form of drug and polymers used in the formulations. The samples were stored at (40±2) °C/75%±5% relative humidity in a stability chamber for 2 months before study. The X-ray generator was set at 40 kV and 35 mA and configured at 2θ geometry[17].

3. Results

In the present study a total of 36 formulations were prepared and the physiochemical properties of prepared buccal patches are shown in Table 2. The thickness of the buccal patches is ranged between (0.2±0.001) and (0.5±0.001) mm and the mass varied from (135.4±0.006) to (166.3±0.006) mg. The pH of the patches are almost neutral and ranged between 6-7, and no mucosal irritation was expected due to neutral pH and showed favorable drug loading efficiency between (18.5±0.4) to (9.5±0.8) mg per patch (3 cm diameter). All the patches showed folding endurance of above 160 and among these 36 formulations, six formulations (FA2, FA8, FA10, FB1, FB14 and FB16) showed high folding endurance of above 250. These patches were selected for further evaluation such as swelling studies, *ex vivo* mucoadhesion time, *ex vivo* mucoadhesive strength, *in vitro* drug release, *ex vivo* permeation, accelerated stability studies and FTIR and XRD spectral studies.

Table 2
Physio chemical characteristics of buccal patches of carbamazepine.

Formulation	Thickness (mm±SD)[a]	Mass uniformity (mg±SD)[a]	Surface pH[a]	Drug content (mg±SD)[a]	Folding endurance (times)[a]
FA1	0.200±0.002	136.400±0.001	6.50±0.110	19.000±0.300	187
FA2	0.400±0.005	140.600±0.002	6.500±0.150	19.100±0.900	255
FA3	0.200±0.004	152.300±0.006	6.700±0.010	18.600±0.100	230
FA4	0.400±0.005	139.400±0.004	7.000±0.050	18.800±0.500	192
FA5	0.300±0.005	140.400±0.007	6.300±0.250	19.000±0.500	198
FA6	0.200±0.005	147.300±0.005	6.400±0.310	18.700±0.800	220
FA7	0.300±0.004	137.300±0.006	7.000±0.180	18.500±0.400	194
FA8	0.200±0.002	142.400±0.005	6.300±0.210	19.500±0.700	253
FA9	0.200±0.006	146.300±0.007	6.500±0.140	19.100±0.900	178
FA10	0.300±0.004	138.400±0.007	6.700±0.180	19.400±0.600	250
FA11	0.300±0.002	139.100±0.007	6.500±0.210	19.000±0.500	212
FA12	0.400±0.004	153.200±0.002	6.600±0.320	18.600±0.400	187
FA13	0.300±0.001	139.400±0.006	7.000±0.420	18.500±0.400	172
FA14	0.300±0.004	136.400±0.006	6.600±0.210	18.300±0.900	200
FA15	0.200±0.001	145.400±0.006	6.400±0.350	18.900±0.600	168
FA16	0.200±0.003	135.400±0.006	6.800±0.060	19.000±0.600	182
FA17	0.200±0.001	143.400±0.006	6.700±0.180	19.100±0.800	210
FA18	0.300±0.007	149.400±0.006	6.300±0.210	19.000±0.600	188
FB1	0.300±0.003	147.400±0.006	6.400±0.310	19.500±0.800	259
FB2	0.400±0.001	146.400±0.003	6.300±0.210	19.000±0.600	185
FB3	0.400±0.006	156.300±0.006	6.300±0.180	18.800±0.800	200
FB4	0.500±0.001	145.400±0.003	6.800±0.180	18.700±0.600	169
FB5	0.200±0.004	143.400±0.006	6.200±0.210	18.300±0.400	210
FB6	0.200±0.004	146.200±0.002	6.400±0.290	18.500±0.600	249
FB7	0.400±0.001	156.300±0.004	6.600±0.030	18.500±0.400	190
FB8	0.300±0.004	153.200±0.002	6.300±0.170	19.000±0.200	188
FB9	0.200±0.004	157.400±0.008	6.400±0.160	18.500±0.400	188
FB10	0.200±0.001	145.400±0.006	6.800±0.050	18.300±0.500	249
FB11	0.200±0.006	156.400±0.003	6.500±0.250	18.900±0.700	186
FB12	0.400±0.001	160.300±0.006	6.900±0.090	19.000±0.700	216
FB13	0.300±0.005	155.400±0.003	6.800±0.110	19.000±0.600	188
FB14	0.200±0.001	148.400±0.006	6.600±0.09	19.100±0.500	268
FB15	0.300±0.005	162.400±0.006	6.700±0.190	18.800±0.500	180
FB16	0.400±0.005	156.200±0.002	6.800±0.21	19.100±0.600	261
FB17	0.400±0.002	166.300±0.006	6.900±0.030	18.500±0.700	197
FB18	0.200±0.001	158.400±0.006	6.500±0.190	18.900±0.600	199

[a]All readings are average of three determinations.

The swelling properties of carbamazepine buccal patches were found to be restrained and varied between the formulations. This could be due to the presence of the hydrophobic and hydrophilic polymers. The swelling behavior of selected carbamazepine patches is illustrated in Figure 1.

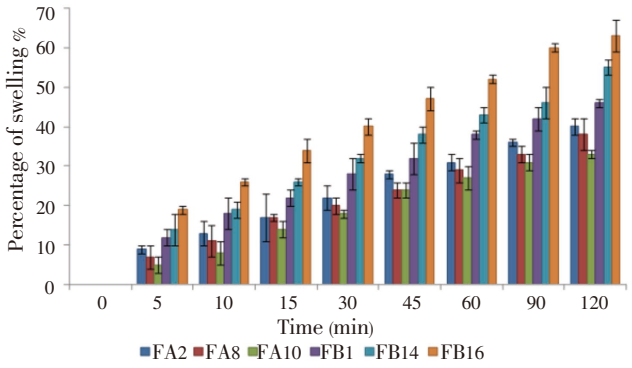

Figure 1. Percentage swelling of selected carbamazepine buccal patches.

The percentage of swelling was higher up to (63%±4%) for FB16 after 120 min. The percentage swelling was increased in the following order, FA10<FA8<FA2<FB1<FB14<FB16. The difference in swelling of the hydrophilic polymers may be due to the difference in resistance of matrix network structure to the movement of water molecule. It was observed that patches with PEG-400 showed more swelling compared to those with PG, and this may be due to higher water uptake of PEG-400 compared to PG. The swelling behavior provides an indication of the relative moisture intake capacities of polymers and whether the formulations continue their integrity after absorption of moisture. While considering the fact that the formulation FA2, FA8 and FB1 contained one part of ethylcellulose and assuming that the effect of ethylcellulose in swelling of the patches as common can be neglected. Although the swelling was high the patches did not illustrate any significant variation in their nature.

The *ex vivo* mucoadhesion time of selected patches was ranged between 109 to 126 min. None of the patches were detached over the study period from the mucosal membrane and this indicated that this period of time was sufficient to retain the patch on the mucosal membrane.

The *ex vivo* mucoadhesive force of selected formulations was obtained in the range of 0.278 to 0.479 Kg/m/s. The highest mucoadhesive force was observed with formulation FB14 (Table 3). Increases in swelling behavior, molecular weight and contact time with mucin network are directly proportional to mucoadhesive property of polymers. Increased mucoadhesive strength in formulations FB14 and FB16 which contain HPMC and PVA may be related to hydrogen bond formation with mucin. High water uptake of PEG-400 used patches shows increased mucoadhesion due to increased interpenetration of polymer and mucin chain at the interface.

Table 3

Ex vivo mucoadhesion study of buccal patches of carbamazepine.

Formulation	*Ex vivo* mucoadhesion time (min)[a,b]	*Ex vivo* mucoadhesive force (Kg/m/s)[a,b]
FA2	112±4	0.341
FA8	110±2	0.321
FA10	109±1	0.278
FB1	120± 3	0.390
FB14	126±3	0.479
FB16	122±4	0.416

[a]All readings are average of three determinations.
[b]Only selected formulations were evaluated.

In vitro release revealed that formulation FB16 showed maximum release of 99.8% after 60 min and FB14 and FA10 showed maximum release after 90 min. But the formulation prepared with ethylcellulose (FA2, FA8 and FB1) showed maximum release after 120 min (Figure 2).

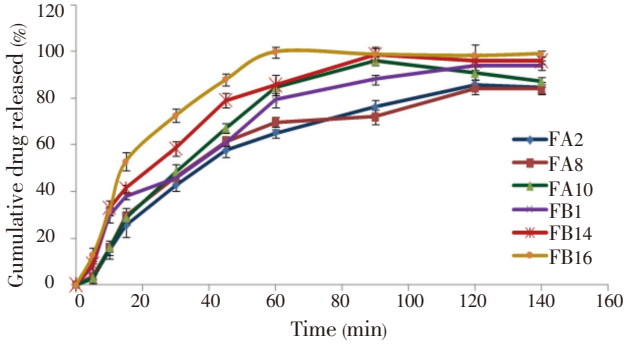

Figure 2. *In vitro* release of selected carbamazepine buccal patches.

From the *in vitro* release studies it was concluded that

Table 4

In vitro release kinetics and drug release mechanism from carbamazepine buccal patches.

Formulations[a,b]	Zero order		First order		Higuchi		Korsmeyer-Peppas Model		Mechanism of drug release
	R^2	k_0	R^2	k_1	R^2	k ($min^{-1/2}$)	R^2	n	
FA2	0.8700	0.6188	0.5487	0.0100	0.9722	8.5446	0.9384	0.9571	Diffusion
FA8	0.8282	0.5914	0.5182	0.0095	0.9515	8.1618	0.9328	0.9319	Diffusion
FA10	0.7768	0.6699	0.5223	0.0102	0.9549	8.2277	0.9250	0.9890	Diffusion
FB1	0.8457	0.6443	0.4710	0.0086	0.9416	9.2680	0.9102	0.8769	Diffusion
FB14	0.7598	0.6491	0.4317	0.0084	0.9217	9.1504	0.8938	0.8826	Diffusion
FB16	0.6675	0.6318	0.3871	0.0079	0.8642	9.1999	0.8665	0.8676	Non-fickian diffusion

[a] All readings are average of three determinations.
[b] Only selected formulations where evaluated.

the patches prepared with PEG-400 showed maximum release while compared with those patches prepared with PG as plasticizer. The *in vitro* release profile of carbamazepine buccal patches is shown in Figure 3. Initially all the patches showed an erratic drug release and were not ideal for a controlled drug delivery system.

The formulation FA2, FA8, FA10, FB1 and FB14 provided best fit to the Higuchi model with R^2 value of 0.9722, 0.9515, 0.9549, 0.9416 and 0.9217 respectively (Table 4). The drug release from carbamazepine buccal patches may be controlled by diffusion. But the formulation FB16 showed good fit to the Korsmeyer-Peppas model with R^2 value of 0.8665 and followed non-fickian (n value 0.8676) drug release varies with time according to the power law. A relative contribution of erosion and diffusion to the overall release mechanism is observed. Since all the tested patches had hydrophilic and hydrophobic polymers, we could not show a relationship to the difference in mechanism of drug release with the polymer properties[18].

Figure 3. shows the *ex vivo* permeation of carbamazepine from different patches. A maximum of 98.99% over a period of 60 min from the formulation FB16 followed by FB14 (at 150 min), FA10 (at 90 min), FB1 (at 120 min) and FA2 and FA8 (at 120 min) showed maximum permeation. The result indicated that maximum of drug is permeated through porcine buccal mucosa and hence could permeate the human buccal membrane.

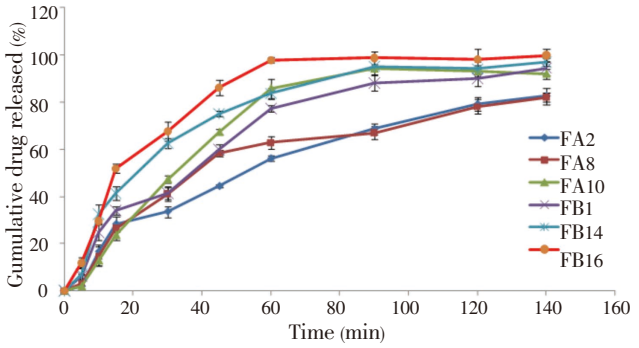

Figure 3. *Ex vivo* permeation of selected carbamazepine buccal patches.

Histopathology examination of integrity and appearance of the porcine mucosal surfaces was done. Porcine buccal mucosa kept in isotonic phosphate buffer (pH 7.4) for 8 h showed a thin keratinized layer of normal stratified squamous epithelium with regular horizontally arranged nuclei. This is compared with the specimens treated with ethanol and isotonic phosphate buffer (pH 7.4) mixture (20:80) for 8 h. The results showed no significant histological changes. This study proved that there was no dramatic alteration in the barrier property and permeation behaviour of the porcine buccal mucosa during *ex vivo* permeation study of carbamazepine (Figure 4).

Table 5
Accelerated stability studies of selected formulations.

Evaluation Parameter	Formulation[a,b] code	1st month	2nd month	3rd month	5th month	6th month
Drug content (mg)[a]	FA2	18.80±0.50	18.80±0.20	18.80±0.70	18.70±0.50	18.80±0.30
	FA8	19.10±0.60	19.20±0.10	19.00±0.30	19.10±0.40	18.40±0.80
	FA10	19.20±0.10	19.40±0.50	19.50±0.10	19.30±0.10	19.00±0.10
	FB1	19.40±0.40	18.70±0.60	18.60±0.50	18.70±0.60	18.80±0.60
	FB14	19.30±0.70	19.80±0.40	19.50±0.70	19.60±0.90	19.10±0.40
	FB16	19.30±0.40	19.60±0.40	19.20±0.10	19.10±0.40	19.30±0.80
Ex vivo mucoadhesion time (min)[a]	FA2	108.00±2.30	107.00±4.00	106.00±2.10	105.00±4.20	103.00±2.30
	FA8	104.00±1.30	102.00±0.50	102.00±2.20	100.00±4.10	100.00±2.30
	FA10	118.00±3.20	114.00±0.60	113.00±2.40	112.00±3.10	111.00±4.40
	FB1	115.00±3.70	113.00±1.80	112.00±2.10	110.00±2.70	109.00±2.90
	FB14	123.00±2.40	121.00±3.80	120.00±2.30	119.00±2.20	119.00±1.20
	FB16	129.00±2.90	127.00±4.10	126.00±3.40	124.00±2.00	122.00±3.20
Surface pH	FA2	6.50±0.24	6.40±0.13	6.30±0.06	6.40±0.25	6.60±0.14
	FA8	6.30±0.14	6.40±0.72	6.50±0.42	6.50±0.19	6.60±0.01
	FA10	6.70±0.32	6.50±0.09	6.40±0.21	6.50±0.99	6.50±0.90
	FB1	6.40±0.11	6.60±0.26	6.50±0.18	6.40±0.13	6.50±1.20
	FB14	6.60±0.20	6.50±0.18	6.50±0.05	6.40±0.14	6.30±0.11
	FB16	6.80±0.17	6.70±0.54	6.50±0.35	6.60±0.01	6.70±0.07
Colour and Appearance	FA2	No change	No change	No change	No change	No change
	FA8	No change	No change	No change	No change	No change
	FA10	No change	No change	No change	No change	No change
	FB1	No change	No change	No change	No change	No change
	FB14	No change	No change	No change	No change	No change
	FB16	No change	No change	No change	No change	No change

[a] All readings are average of three determinations.
[b] Only selected formulations were evaluated.

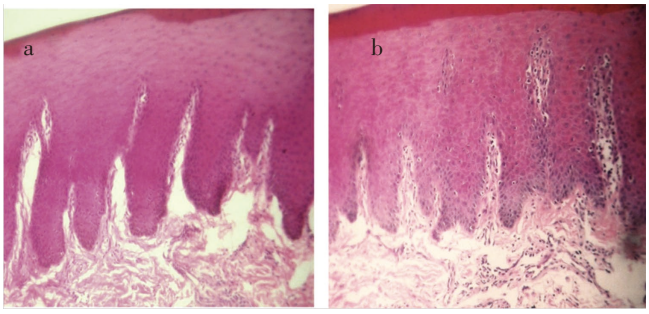

Figure 4. Histopathology of paraffin embedded cross-sections of porcine buccal mucosa.
(a) Porcine buccal mucosa treated with isotonic phosphate buffer (pH 7.4) for 8 h.
(b) Porcine buccal mucosa treated with ethanol and isotonic phosphate buffer (pH 7.4) mixture (20:80) for 8 h.

After the accelerated stability study of carbamazepine buccal patches, the drug content of the patches was ranged between (18.4±0.4) and (19.9±0.4) mg. Mucoadhesion time of patches showed between (101±2.1) to (125±1.3) min. During and at the end of the accelerated stability study, tested patches showed similar drug content, mucoadhesion time and surface pH. Stability studies conducted in normal human saliva shows no abnormal color changes or changes in the texture (Table 5).

In the FTIR spectra of carbamazepine pure sample showed, characteristic peaks at 3472.56, 3005.28, 1661.55, 1661.55 and 1495.08 cm^{-1} were recorded due to N-H, C-H, C=O and C=C stretching respectively. The spectra obtained from the formulations showed that all the principle peaks are at or around the requisite wave number of the pure drug. This confirmed the purity and integrity of the drug in the formulations.

The XRD pattern of formulation FB16 showed less intensity and reduced number of peaks than powder form. This change indicates a reduction in crystallinity and increase in amorphous nature. This may be due to increased solubility of components in the formulation matrix. The distinctive peaks of carbamazepine at 13.48°(2θ), 15.39°(2θ), 25.29°(2θ) and 27.65°(2θ) revealed that the drug is present in crystalline state in the formulation[19].

4. Discussion

Unidirectional mucoadhesive buccal patches of carbamazepine were developed to improve the bioavailability by avoiding the hepatic first pass metabolism, and thereby reducing metabolite dependent adverse drug effect. The *in vitro* release profile reveled that maximum amount of carbamazepine is released from the prepared patches within specified mucoadhesion period and this indicated that the prepared novel unidirectional mucoadhesive buccal patches of carbamazepine would be a potential drug delivery system for systemic delivery of carbamazepine. But in future this has to be confirmed with *in vivo* studies.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgements

The authors wish to express thanks to the Caplin Point Pharma Ltd, Puducherry, India for providing a gift sample of carbamazepine and RR college of Pharmacy (affiliated to Rajiv Gandhi University of Health sciences, Bangalore, India) for providing financial support to perform this study and also express sincere thanks to Dr. Soundrapandian for valuable guidance throughout the research period.

Comments

Background

Epileptic treatment should be patient friendly. Patients in deep sleep and in unconscious state cannot receive treatment by oral route. Suppositories were prepared to meet above needs, but may cause inconvenience and need experience. This research about buccal route of administration of carbamazepine in the form of buccal patches may be a boon for epileptic patients as an alternative route of drug delivery. Moreover this route may by pass hepatic metabolism and metabolite related side effects.

Research frontiers

Carbamazepine is known worldwide for its associated adverse drug reaction, but still used as a drug of choice for neuralgia, bipolar disorder and epilepsy. This research may improve present lacuna in the clinical use of carbamazepine and may be a step next to formulating an alternative route of drug administration.

Related reports

Ex vivo mucoadhesion time, mucoadhesive strength, *in vitro* release study and *ex vivo* permeation study were already reported in many related research papers. But this study including other parameters like histopathological examination of porcine mucosa used for the permeation study and effect of dissolution medium on porcine mucosa. The reports given are interesting. The mechanism of drug release was studied by various drug release models and reported. In this study formulations were designed to release drug completely within mucoadhesion period of patches.

Innovations and breakthroughs

The mucoadhesion time was used to design release profiles of the formulations by altering proportions of polymers to achieve maximum drug release within specified mucoadhesion period. This could be a best alternative method of drug administration rather than oral formulations. The practical problems related to buccal mucoadhesion were also considered. Moreover these formulations by passes hepatic first pass metabolism and associated complications.

Applications

This study proved good mucoadhesive strength and quick release of carbamazepine within specified experimental conditions. The usage of carbamazepine in the form of buccal patches may help to minimize current clinical problems and patient incompatibility.

Peer review

This is a good study about trans buccal administrations of carbamazepine. This study concentrated on various parameters like mucoadhesion time, mucoadhesive strength, *ex vivo* permeation through porcine mucosa and stability studies under human saliva. This covered almost all important parameters to be considered to understand the drug release mechanism from the formulation.

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