Research Article

Design and development of mucoadhesive buccal patches of chlorzoxazone

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ABSTRACT

Aim and Objective: The main purpose of this study was to formulate and evaluate chlorzoxazone mucoadhesive buccal patches, to increase therapeutic efficacy, better bioavailability, and reduce the side effect, and to provide controlled release of drug and improve patient compliance. Chlorzoxazone is used in the treatment of muscle spasm/pain and helps in relaxing the muscles. **Materials and Methods:** Buccal films of chlorzoxazone were prepared by solvent casting technique using film-forming mucoadhesive polymers such as hydroxypropyl methylcellulose and ethyl cellulose with different concentrations. Five different formulations were prepared and evaluated with respect to patch thickness, surface pH, folding endurance, drug content uniformity, swelling index, determination of moisture and moisture absorption, and *in vitro* release study. Compatibility study was carried out by Fourier transform infrared (FT-IR) spectral analysis. **Results and Discussion:** FT-IR study confirmed the absence of any drug/drug-polymer excipient interaction. All the prepared formulations were evaluated. The formulation F2 showed good drug content compared other formulations and in *in vitro* release studies of formulation F2 show better drug release for a period of 4.5 h. F2 shows decrease in drug release with an increase in amount of polymer. Therefore, F2 was selected as best formulation. **Conclusion:** The above study concluded that possibilities of the making of mucoadhesive drug delivery system for chlorzoxazone which will be more efficacious and also having satisfactory sustained release profile which may provide and increased therapeutic efficacy.

KEY WORDS: Buccal patches, Chlorzoxazone, Hydroxypropyl methylcellulose

INTRODUCTION

Novel Drug Delivery System (NDDS)

Many drug delivery and targeting systems are developed to reduce the degradation of drug and harmful side effects and to increase the bioavailability. Among drug carriers, one can name soluble polymers, microparticles made of insoluble or biodegradable natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposome's, and micelles. The carriers can be made slowly degradable, stimuli reactive (e.g., pH or temperature sensitive) and even targeted (e.g., by conjugating them with specific antibodies against certain characteristic components of the area of interest).[1]

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The benefit of the concentration of drug shows the level of toxic and therapeutic benefits; the method by which a drug is delivered can have a significant effect on its efficacy.[2] From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and efficacy of drugs were generated. These new strategies, often called DDS, are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bioconjugate chemistry, and molecular biology.

NDDS is mainly designed to achieve a desire targeted therapeutic effect of drugs and to reduce the toxic effect and side effect. NDDS is based on physical and biochemical mechanism where physical mechanism or controlled DDS includes dissolution, osmosis, erosion, and diffusion. Biochemical mechanism includes gene therapy, liposomes, nanoparticles, and monoclonal antibodies.

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Mucoadhesion

The concept of mucoadhesion was introduced in the field of controlled release DSSs in the early 1980s.[3] Mucoadhesion in newly concept introduced in drug delivery where the bioadhesion attaches the drug carrier system to a specific biological location (epithelial tissue). If adhesive attachment is to a mucous coat, the phenomenon is referred to as mucoadhesion.[4]

Buccal Film

Buccal film is defined as the dosage form which dissolves into the buccal mucosa or mouth and releases the medicament to provide local or systemic drug delivery and employs a water dissolving polymer (hydrocolloid bioadhesive polymer). These polymers allow the dosage form to adhere, hydrate, and dissolve into the mouth.[5] As the strip dissolves, the drug can enter the bloodstream enterically or sublingually.[3] For buccal route of administration, buccal film was recently developed dosage form.

When compared to tablets, buccal films allow easy absorption of drug by quick wetting the film in the large surface area.[6,7]

MATERIALS AND METHODS

Chlorzoxazone was acquired from Tentra Chemie. Hydroxypropyl methylcellulose (HPMC) was obtained from Indian Research Product. Further, all instruments and chemical reagents used for the experiment studies are possibly best Pharma grade.

Preparation of Chlorzoxazone Mucoadhesive Buccal Patches

Solvent casting technique has been used for preparing buccal patches of chlorzoxazone, Table 1. HPMC was weighed (200 mg) correctly which was allowed to dissolve in 2 ml of ethanol containing beaker. Polymers were allowed to swell for 5 min in the beaker containing ethanol. To the polymer solution, again 3 ml of ethanol were added and stirred after that add slowly one or two drops of propylene glycol to the polymer solution. Simultaneously, chlorzoxazone was exactly weighed in quantity and diluted in 1 ml of ethanol in a different beaker. Mix the drug and polymer solution by using magnetic stirrer. Then, it was transferred into a glass Petri dish, to avoid sudden evaporation inverted funnel was kept on Petri dish[8]. The polymeric solution was allowed to dry for 12 h in room condition. After drying, films were observed and checked thoroughly. It was further allowed for evaluation tests for selecting the best characteristics. Similarly, films of F1, F2, F3, F4, and F5 are prepared in different ratios of ingredients.[9]

Physicochemical Evaluation of Prepared Mucoadhesive Buccal Patches

Patch thickness

A micrometer screw gauge was used to measure the thickness of the patches and the mean value is calculated and recorded correctly.[10,11]

Surface pH

To determine the surface pH, the formulation was swelled on agar plates for 2 h which is measured by pH paper by placing it on swollen surface of patches. The mean was calculated and recorded.[12]

Folding endurance test

The patches of each formulation were continually folded at the same place for maximum number of times until it gets break to determine the folding endurances. The number of folding was calculated and recorded if the patches remain the same even after maximum number of folds.[13]

Estimation of drug content

The drug content of patches was determined without the backing membrane. The patches were dissolved in hydrochloric acid beaker and brought the volume up to 10 ml with distilled water. After dispersion of patches in 5 ml of above solution, it is then allowed to dissolve in phosphate buffer saline pH 6.8; then, it is shaken vigorously for 24 h at room temperature. After sometime, it is filtered using Whatman filter paper (No. 42). To determine the drug content, 1 ml of sample solution is analyzed by ultraviolet (UV) spectroscopy at 280 nm.[14,15]

Swelling index

Using diameter method, swelling index of the patches can be determined. Agar solution was used to swell the patches which can be done by dissolving 0.2 g of agar in 10 ml warm simulated saliva fluid, pH 6.8 (50–70°C). It is allowed to pour in a Petri dish and cool it. The initial patch diameter was recorded

Table 1: Formulation of chlorzoxazone mucoadhesive buccal patches

Ingredients (mg)	F1 (1:1)	F2 (1:2)	F3 (1:1)	F4 (1:2)	F5 (1:2)
Drug	100	100	100	100	100
Hydroxyl methylcellulose	100	200	-	-	-
Ethyl cellulose	-	-	100	200	-
Hydroxyl methylcellulose and ethyl cellulose	-	-	-	-	200
Ethanol	5 ml	5 ml	5 ml	5 ml	5 ml
Propylene glycol	0.5 ml	0.5 ml	0.5 ml	0.5 ml	0.5 ml

and each patch was allowed to swell to determine the final patch diameter. The percentage swelling (%S) was calculated using the following equation:

$$\%S = (wt–wt0/wt0)*100$$

Where,
%S – swelling index
Wt – Initial weight of patch
W0 – final weight of patch

Determination of Moisture Content and Moisture Adsorption

The patches were weighed correctly and placed in the desiccators containing anhydrous calcium chloride [16] After 3 days, the patches were taken out and weighed. The moisture content (%) was determined by calculating moisture loss using the formula:

Moisture loss (%): Initial weight−Final weight/Initial weight × 100

For determining the moisture absorption, the patches were weighed accurately and placed in the desiccators containing saturated solution of aluminum chloride, which maintains 76% and 86% relative humidity. After 3 days, the films were taken out and weighed.[14] The percentage moisture adsorption was calculated using the formula:

Moisture absorption (%): Final weight−Initial weight/Initial weight × 100

In vitro Release Study

Franz diffusion cell was used for *in vitro* drug release study. There are two compartments (donor and receptor) in between the donor and receptor compartment; the patches were applied on dialysis membrane, wherein receptor compartment, phosphate buffer saline pH 6.8 was filled (40 ml). Using magnetic stirrer, it was stirred at 50 rpm and started releasing at 37 ± 0.5°C. At an equal interval of time, 5 ml of sample was withdrawn and replaced with same buffer solution. The amount of drug released is determined using UV spectrophotometer at 280 nm against a blank.[17,18]

Compatibility Studies

Fourier-transform infrared (FT-IR) spectroscopy

IR spectral analysis was mainly done to analysis the pure and highest proportion among the polymers. It is mainly used to determine the interactions between varies polymers, drugs, and excipients. Here, the drug and excipients should be compatible with one another to have a stable, safe, and efficacious. IR spectral analysis of pure drug and highest proportion of polymers (Drug: polymer ratio is 1:2) was carried out.[19]

The peaks and patterns produced by the pure drug were compared with the peaks and patterns of the combination of drug and polymers.[20]

The FT-IR analysis was conducted for the structure characterization; FT-IR spectra were recorded on Bomem FT-IR MB II spectrophotometer. Test samples were mixed with KBr, pressed into a pellet, and scanned from 3300 to 777.29 cm^{-1}.

RESULTS AND DISCUSSION

The present study was undertaken to formulate mucoadhesive buccal patches using two polymers with different ratios and prepared by solvent casting method. The prepared patches are subjected to evaluation studies such as surface pH, patch thickness, folding endurance, estimation of drug content, swelling index, determination of moisture content and moisture adsorption, *in vitro* release study, and IR studies. The studies performed and results are presented.

IR spectroscopy

The IR studies of pure chlorzoxazone and formulation containing highest proportion of the polymer (1:2) were

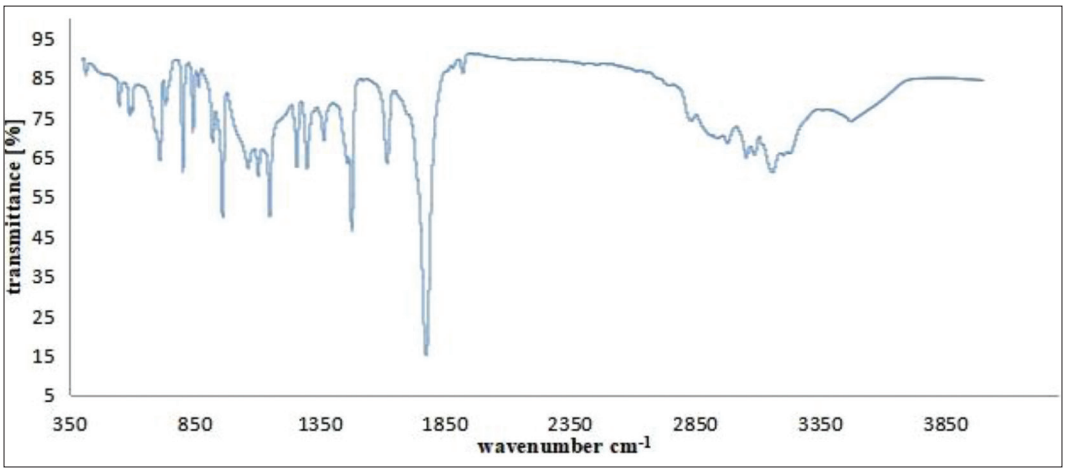

Figure 1: IR Spectrum of chlorzoxzone

carried out to study the interaction between the drug and polymers. The results are shown in Figures 1-3.

OH stretching, CH aliphatic stretching, C=O stretching, C=stretching methylenic, CH_2 stretching, OH bending, and aromatic vibration bending of pure chlorzoxazone and the chlorzoxazone formulation containing higher proportion of the polymer were almost in the same region of wavenumber ranging from 3300 to 777.29 cm^{-1}.

The IR spectrum of pure chlorzoxazone and chlorzoxazone formulation containing highest proportion of polymer showed similar fundamental peaks and patterns. The result proved that they were no significant interaction between the drug and polymers.

Thickness of Patch

The thickness of all the prepared formulated buccal patches was from 0.13 to 0.26 mm. The data are presented in Table 2.

Surface pH

The surface pH of all developed formulations was found to be in between 6.2 and 6.7. It represents the better patient acceptability. The data are presented in Table 2.

Folding Endurance

The folding endurance of all prepared formulation was within the range of 92–130. The values are presented in Table 2.

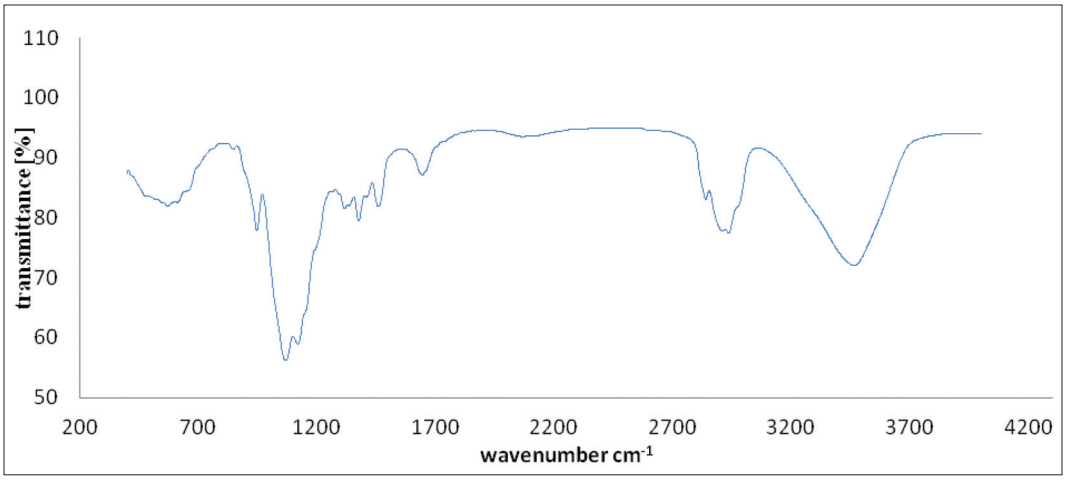

Figure 2: IR Spectrum of HPMC

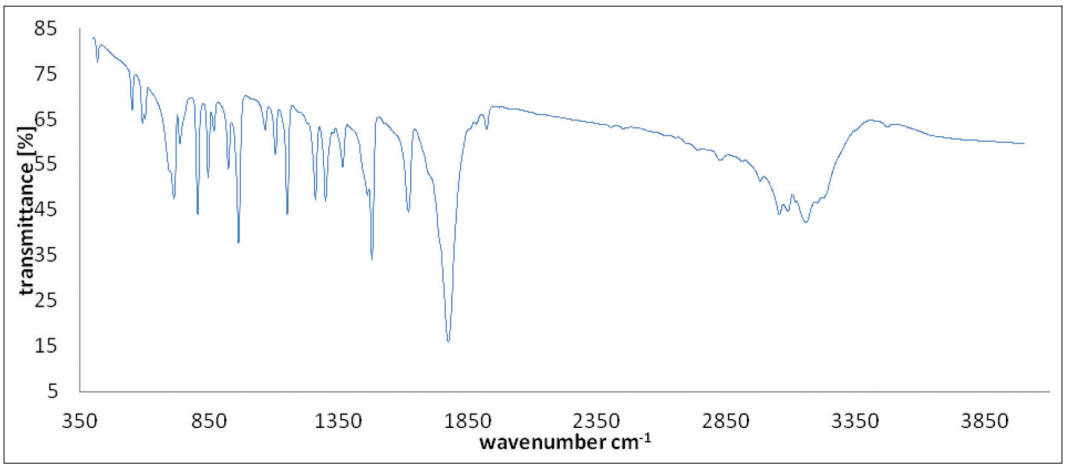

Figure 3: IR Spectrum of HPMC + chlorzoxzone

Table 2: Characteristics of buccal mucoadhesive patches containing chlorzoxazone

Formulation	Thickness (mm)	Weight (g)	Surface pH	Drug content (mg)	Folding endurance
F1	0.16±0.01	0.0045±0.0021	6	98.76±0.46	120
F2	0.26±0.03	0.0070±0.0017	6.5	99.74±0.42	130
F3	0.18±0.05	0.0063±0.0002	6.4	98.64±0.47	126
F4	0.13±0.03	0.0078±0.0016	6.2	98.87±0.56	104
F5	0.22±0.01	0.0084±0.0008	6.6	99.64±0.50	92

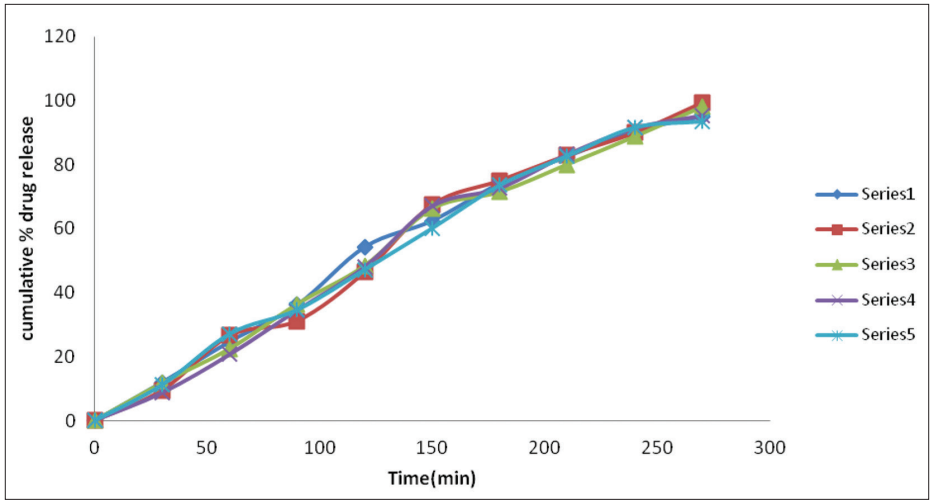

Figure 4: Comparitive dissolution study of different formulation with various ratios of polymers

Table 3: Percentage of swelling index in time (h)

Time	F1	F2	F3	F4	F5
30 min	23.7±0.05	62.1±0.03	30±0.01	64.5±0.2	74.5±0.03
60 min	50.8±0.02	74.2±0.04	-	-	-
120 min	-	89.2±0.02	-	-	-

Estimation of Drug Content

The drug content uniformity of all formulation was carried out, the drug content was found to be in between 98.64% and 99.74%. The values are given in Table 2.

Swelling Index

The swelling behavior of formulation shows its bioadhesive property and drug release of the formulation is determined at various time intervals. It is observed that the formulation F2 showed highest swelling index due to greater swelling of HPMC. It indicates that when patches placed in an aqueous medium, liquid penetrates into a patch and a gel is formed. The data are presented in Table 3.

Moisture Content of Chlorzoxazone

The moisture content percentage was found to be increased with the increasing concentration of polymers. The values are given in Table 4. Lower the moisture content better the protection from the bacterial contamination and bulkiness of patches and also help to remain stable from being completely dried.

In vitro Study

Diffusion cell was used for the *in vitro* dissolution study using phosphate buffer pH 6.8. All the formulation results are shown in Table 5. The graphical representation of data is shown in Figure 4.

The percentage drug release of all formulations after 4.5 h using HPMC and ethyl cellulose was found to be F1 (94.89%), F2 (99.34%), F3 (99.01%), F4 (95.43%), and F5 (93.41%), respectively. The *in vitro* release of chlorzoxazone buccal patch F2 showed decrease in drug release with an increase in amount of polymer.

Table 4: Moisture content of chlorzoxazone buccal patches (F1–F5)

Formulations	Moisture content (%)	Moisture uptakes (%) (76% RH)
F1	1.32±0.01	4.04±0.05
F2	1.45±0.02	4.24±0.08
F3	1.48±0.01	3.86±0.07
F4	0.97±0.01	3.53±0.06
F5	1.04±0.01	4.88±0.05

Table 5: Comparative dissolution study of different formulations with various ratios of polymers

Time	% drug release				
	F1	F2	F3	F4	F5
30	11.96	9.54	11.75	8.7	11.21
60	24.66	26.6	22.47	20.71	27.1
90	36.14	31.14	36.41	34.55	34.6
120	54.21	46.45	48.43	48.14	47.15
150	62.4	67.5	66.21	67.1	60.1
180	74.02	75.01	71.41	72.72	73.54
210	82.45	82.96	80.01	83.24	82.65
240	90.41	89.96	88.71	91.49	91.56
270	94.89	99.34	98.01	95.43	93.41

DISCUSSION

The present work has been made to develop the sustain release mucoadhesive buccal patch of chlorzoxazone prepared by solvent casting technique using HPMC,

ethyl cellulose in different ratios to produce the desire therapeutic dose of drug.

FT-IR study confirmed the absence of any drug/drug-polymer excipient interaction. F2 showed good drug content compared other formulations and in *in vitro* release studies of formulation F2 have good drug release for a duration of 4.5 h show better drug release for a period of 4.5 h. F2 shows increase in amount of polymer and decrease in drug release. Therefore, F2 was selected as best formulation.

It was revealed that polymer ratio had a significant influence on drug release. Thus, stable dosage form can be developed for chlorzoxazone for sustained release by buccal patches.

CONCLUSION

In the present study, an attempt is made to develop a novel mucoadhesive DDS in the form of buccal patches for the release of chlorzoxazone to maintain constant therapeutic level of drug for long time.

These mucoadhesive buccal patches were displaying sufficient bioadhesive strength and *in vitro* drug release. The enhanced patch F2 with a ratio of 1:2 exhibited an increased bioavailability when compared to other polymers. From the above results, it is concluded that HPMC can be used to formulate chlorzoxazone mucoadhesive buccal patches.

The above study concluded that possibilities of the making of mucoadhesive DDS for chlorzoxazone which will be more effective and also having satisfactory sustained release profile which may provide and increased therapeutic efficacy.

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