INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

DESIGN, DEVELOPMENT AND EVALUATION OF BUCCAL MUCOADHESIVE PATCH OF DEXAMETHASONE SODIUM PHOSPHATE FOR THE MANAGEMENT OF ORAL SUBMUCOUS FIBROSIS, ULCERATION AND LICHEN PLANUS

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ARTICLE INFO

Article history

Received 18/07/2019

Available online

31/07/2019

Keywords

OSMF,

Mucoadhesive,

Swelling Index Etc.

ABSTRACT

The objective of the present study was to develop mucoadhesive buccal patch of Dexamethasone for the treatment of oral submucous fibrosis. In formulation, chitosan is used as a polymer and PEG 400 as a plasticizer. Backing membrane was prepared by using ethyl cellulose and isopropyl alcohol. The solvent casting method was used for the preparation of mucoadhesive buccal patch as it is cost effective and efficient method. Preformulation studies of Dexamethasone were carried out. FTIR studies implied that there were no interactions between drug and polymers. The prepared batches were evaluated for visual appearance, thickness, folding endurance, weight variation, swelling index, surface pH, mucoadhesive time, % drug content, in-vitro diffusion and ex-vivo permeation study. Total nine batches of Dexamethasone mucoadhesive buccal patch were prepared successfully using chitosan as a polymer and PEG 400 as a plasticizer by solvent casting method. Based on results batch F2 was selected as optimized formulation. From invitro release of batches, F2 was found best, showing release of drug 64.53% in 4 hours. A clinical examination of the oral cavity was carried out under artificial light which includes extra oral examination and intra oral examination. The results of the present study of mucoadhesive semi-solid drug design for the treatment of OSMF will be useful for drug industry for the benefit of patients suffering from OSMF. The most important advantage of the Mucoadhesive buccal films is that it contains a lower drug dose, adequate for therapeutic effect as it is placed directly on the site of the inflammation, when compared to conventional administration. Moreover, this Mucoadhesive buccal patch is very convenient because it is non-irritant and self-administration is possible. Given promising therapeutic effects, the buccal film developed here could become a local drug delivery device for management of oral submucous fibrosis, ulceration and lichen planus.

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*Please cite this article in press as **Satish Polshettiwar** et al. Design, Development And Evaluation of Buccal Mucoadhesive Patch of Dexamethasone Sodium Phosphate for the Management of Oral Submucous Fibrosis, Ulceration and Lichen Planus. Indo American Journal of Pharmaceutical Research.2019:9(07).*

INTRODUCTION

Oral sub mucous fibrosis is a chronic debilitating disease of the oral cavity characterized by inflammation and progressive fibrosis of the sub mucosal tissues (lamina propria and deeper connective tissues). Oral submucous fibrosis results in marked rigidity and an eventual inability to open the mouth. The buccal mucosa is the most commonly involved site, but any part of the oral cavity can be involved, even the pharynx. Worldwide, estimates of oral submucous fibrosis indicate that 2.5 million people are affected, with most cases concentrated on the Indian subcontinent, especially southern India. The rate varies from 0.2-2.3% in males and 1.2-4.57% in females in Indian community.[1] Oral submucous fibrosis also has a significant mortality rate because it can transform into oral cancer, particularly squamous cell carcinoma (Reported cases of 7.6% worldwide)[2-4]. Different classes of drugs such as corticosteroids, extravasations antidotes, interferon, antioxidant, and vasodilator are given to reduce morbidity and to prevent complications which appear due to submucous fibrosis [1]

Dexamethasone is a glucocorticoid agonist. Dexamethasone crosses cell membranes and binds with high affinity to glucocorticoid receptors. This complex binds to DNA elements (glucocorticoid response elements) which results in a modification of transcription and hence, protein synthesis in order to achieve inhibition of leukocyte infiltration at the site of inflammation, suppression of humoral immune responses, and reduction in edema It has several side effects but still it is being frequently used in the treatment of submucous fibrosis. The conventional treatment with injections was found to be hazardous, whereas the conservative treatment with buccal patches and gel were found to be safe [2]. Also the parenteral formulation is invasive, causes pain and decreased patient compliance. Retentive buccal mucoadhesive formulations may prove to be a viable alternative to the conventional medications as they can be readily attached to the buccal cavity, retained for a longer period of time and removed at any time [,3,4,5]

Earlier also attempts have been made to formulate various mucoadhesive devices including tablets, films, patches, disks, strips, ointments, and gels. Buccal patches are highly flexible and thus much more readily tolerated by the patient than tablets. Patches also ensure more accurate dosing of the drug compared to gels and ointments [6]. Hence present study was aimed to formulate the buccal patch of Dexamethasone sodium phosphate to overcome the side effects of the injection and also ensure satisfactory level of drug release in the oral cavity for a period of treatment

For management of OSMF, intralesional steroids have been routinely used with fairly good results. The disadvantage with intralesional steroid is, it requires multiple injections which causes unnecessary trauma to the already inflamed area and therefore the treatment with injections is very painful, whereas the treatment with buccal patches is safe and convenient.

uccal patches are highly flexible and thus much more readily tolerated by the patient than tablets. Patches also ensure more accurate dosing of the drug compared to gels and ointments. Hence to overcome the side effects of the injections and tablets buccal patch of Dexamethasone is prepared. [7,8,9]

MATERIALS AND METHODS

Dexamethasone Sodium Phosphate was purchased from yarrow chem Ltd. (Mumbai, India). Chitosan and chloroform were obtained from Loba chemie Pvt. Ltd. (Mumbai, India) and carbopol 940P was obtained from S.D. fine chemicals, (Mumbai, India). Dibutyl phthalate and Ethanol were obtained from Merck specialties Private Limited, (Mumbai, India). Polyethylene glycol 1000 was obtained from Neeta chemicals Ltd., (Pune). Aspartame was obtained from HiMedia laboratories Pvt. Ltd. (Mumbai, India). All other chemicals used were of analytical grade and procured from S.D. Fine Chemicals (Mumbai, India), Mouth mirror ,probe, metallic scale, divider, normal syringe, gloves and 26 gauge 1.5 inch needle. Injectable Dexamethasone (4 mg in 2ml vials).

Experimental design

A 3^2 full factorial design was used to prepare formulation by taking Chitosan and PEG 400 as independent variable and thickness, weight variation and surface pH as dependant variables. Following batches were developed. [10,11,12]

Table 1: Factors and Levels in 3^2 factorial design runs.

Coded values	Actual values	
	Chitosan (%) X_1	Polyethylene glycol 400 (%) X_2
-1	1	1
0	2	2
1	3	3

Table 2: Experimental design.

Experimental conditions	Coded values		Actual Values	
	X_1	X_2	X_1(%)	X_2 (r %)
F1	-1	-1	1	1
F2	0	-1	2	1
F3	+1	-1	3	1
F4	-1	0	1	2
F5	0	0	2	2
F6	+1	0	3	2
F7	+1	+1	1	3
F8	0	+1	2	3
F9	+1	+1	3	3

Preparation of mucoadhesive patches

The films of respective composition were devised using **Chitosan** as polymer [14,15], Polyethylene glycol (PEG) 400 as plasticizer, aspartame and peppermint oil as sweetening and flavouring agents along with drug and solvent. The solvent system used was 50:50 ratio of ethanol and chloroform. The polymers, PEG 400 and aspartame were weighed accurately and dissolved in solvent mixture to obtain a viscous solution. The drug was then dispersed uniformly in the viscous solution with continuous mixing on magnetic stirrer. In order to avoid entrapment of the air bubble inside the film, the entire drug-polymer-solvent system was subjected to vacuum treatment with the aid of vacuum desiccator. Then the solution was poured into moulds lined with aluminum foil for casting and dried for a period of 24 h. Placebo films without the drug were also prepared as mentioned above. After drying medicated patches of 2×2 cm^2 area were cut using a sterile stainless steel borer, each film containing 2.0 mg of drug. The cut patches were used for further studies [16]

The composition of different patches is given in table 3.

Table 3: Optimization of Dexamethasone loaded buccal patch.

Formulation Code	Drug (mg)	Chitosan (%)	PEG 400 (%)	Glycerine (%)	Methanol (ml)
F1	4	1	1	1	10
F2	4	2	1	1	10
F3	4	3	1	1	10
F4	4	1	2	1	10
F5	4	2	2	1	10
F6	4	3	2	1	10
F7	4	1	3	1	10
F8	4	2	3	1	10
F9	4	3	3	1	10

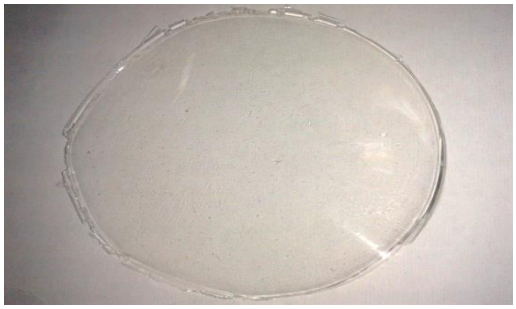


Fig. 1. Backing membrane.

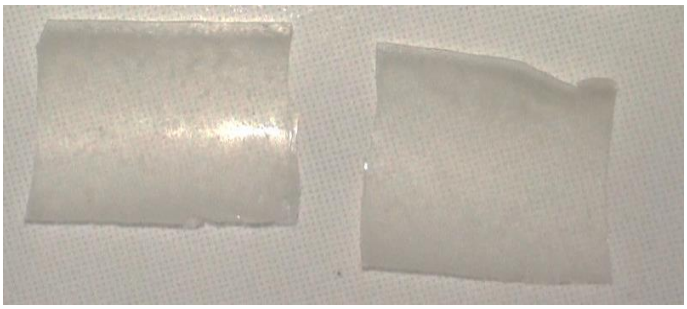


Fig.2 Dexamethasone loaded buccal patch.

Drug excipient compatibility studies

Infrared spectroscopy was studied using a Shimadzu FTIR 8300 Spectrophotometer and the spectrum was recorded in the region of 2000 to 400 cm-1. The process consisted of dispersing a sample (drug, drug-polymer mixture and patch) in KBr (200-400 mg) and compressing into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was obtained. The spectra obtained for drug, physical mixture of drug with polymer and patch was compared [16,17]

Physicochemical characterization of buccal mucoadhesive patches

Weight variation

Weight variation test was carried out using digital balance (Mettler Toledo), by weighing three films containing a specific amount of drug from each formulation. The standard deviations (SD) were calculated from individual weight of the film [17,18.]

Film thickness

Thickness of films was evaluated by using a puncture test and texture analyzer (Instron® 3366- 2716015, Germany). Ten readings were taken and the mean thickness was calculated. The standard deviations (SD) were calculated from individual data value.

Content uniformity of patches

To make sure uniform distribution of BSP in film, a content uniformity test was performed. The film was added to 100 ml of sorensons phosphate buffer (SPB) pH 6.4 contained in a 250 ml beaker was placed on temperature controlled magnetic stirrer maintained at 37 °C. The medium was stirred at 300 rpm with a Teflon coated magnetic bead for 3 h. Then the solution was filtered through 0.45 µm membrane filter and the filtrate was examined for the drug content at 242 nm using UV-Spectrophotometer [17, 19.]

Surface pH study

The surface pH of the patch was determined in order to investigate the possibility of any side effects (in-vivo). A combined glass electrode was used for this purpose. The patches were allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.5 ± 0.2) for 15 minutes at room temperature, and pH was noted down by bringing the electrode in contact with the surface of the patch and allowing it to equilibrate for 1 minute [17]

Percentage moisture absorption

The percentage moisture absorption test was carried out to ensure physical stability or integrity of buccal films. Buccal films were weighed and placed in a desiccator containing 100 ml of saturated solution of aluminum chloride and 75 ± 5% RH was maintained. After three days the buccal films were taken out and reweighed. The percentage moisture absorption was calculated using this formula [17, 19]

Percentage moisture loss

The percentage moisture loss was carried out to evaluate integrity of the film in dry conditions. Buccal films were weighed and kept in a desiccator containing anhydrous calcium chloride. After three days, the patches were taken out and reweighed. The percentage moisture loss was calculated using the formula [17, 19]

Tensile strength

Area of the films and maximum load which film can tolerate were measured using a puncture test and texture analyzer (Instron® 3366-2716015, Germany) (n = 3). Film specimens were mounted on a film holder. The puncture probe was driven through the film at a speed of 0.1 mm/s. Force vs. displacement curves were recorded with a 50 N load cell. Load versus displacement curves were recorded until rupture of the film and used to determine the tensile strength of films and backing membrane [17, 24.]

Folding endurance

A small strip of film was cut evenly and separately folded at the same place until it broke. The number of times the film could be folded at the same place without breaking gives the folding endurance [17, 19]

In vivo residence time

In vivo residence time of placebo buccal patch was carried out in healthy human volunteers as subjects (aged 22–30 years, n=4). BSP have some side effect like Hypertension, oedema, increased susceptibility to all kinds of infection, spontaneous fractures, nitrogen depletion etc., so to avoid all these side effect placebo buccal patches were used for *in vivo* residence time study.

The experiment was carried out with drug free films. Prior to the test, the volunteers were educated with the procedure and purpose of test. They were asked to rinse their mouth with distilled water before a piece of the drug free patch with water impermeable backing membrane was placed on their buccal mucosa. The bioadhesive film was placed on the buccal mucosa between the cheek and gingiva in the region of the upper canine and gently pressed onto the mucosa for about 30 sec. The film and the inner upper lip were carefully moistened with saliva to prevent film from sticking to the lip. The subjects were not allowed to eat or drink during the study (1 h). They were asked to monitor the ease with which the system was retained on the mucosa and note any tendency to detachment. The adhesion time was indicated by either complete erosion of the film or failure of the adhesive bond. Any complaints and bad feelings were also recorded. The study was repeated after two days on same volunteers [16,19]

In vitro release study

As there was no official method prescribed for in vitro drug release studies of buccal patch, a simple in-house laboratory assembly was utilized simulating the conditions of oral cavity. The backing membrane with mucoadhesive patches (2×2 cm2 equivalent to 2.0 mg BSP) were carefully pressed on to a glass slide with a few drop of the adhesive and left for a minute for the adherence of backing membrane onto the slide. The slide with the adhered mucoadhesive dosage form was then placed into a 100 ml beaker containing 80 ml of SPB pH 6.4, which was pre heated to 37 ± 0.5 ºC.

Then the beaker was kept on the temperature controlled magnetic stirrer maintained at temperature at 37 ± 0.5 º C and the medium was stirred at 50 rpm with the help of small teflon coated magnetic bead. The beaker was kept covered throughout the study to preclude evaporation of the medium. Five ml of sample were collected at various time intervals of 5, 10, 15, 30, 45 and 60 min and replaced by the same volume of the buffer. These samples were filtered through 0.45 µm membrane filter and the filtrate was used for estimation of drug concentration by using a UV spectrophotometer at a wavelength of 242 nm. Three patches of each formulation were tested.

The in-vitro residence time

It was determined using a locally modified USP disintegration apparatus (Disintegration tester, Electrolab, Mumbai, India). The disintegration medium was composed of 900 ml of SPB pH 6.4 maintained at temperature 37 ± 2 °C. A segment of pig buccal mucosa, 3 cm long, was glued to the surface of a glass slab, vertically attached to the apparatus. The mucoadhesive film with backing membrane was hydrated from film surface using 15 µl SPB pH 6.4 and then the hydrated surface were brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down so that the film was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time necessary for complete erosion or detachment of the film from the mucosal surface was recorded (mean of triplicate determinations) [16,17]

***In vitro* drug release studies**

The release profile of formulation F1 to F5 which contain different concentration of Chitosan is illustrated in (Fig 1). The cumulative percent drug release from the formulations F1,F2, F3, F4 and F5 was found to be 97.42 ± 3.77, 94.55 ± 2.4, 88.59 ± 2.74, 68.96 ± 3.42 and 57.89 ± 2.42 at the end of 30 minutes. It was found that increase in the concentration of Chitosan significantly decreased the drug release. The slow drug release mechanism for higher polymer concentration can be explained by reduction in permeability due to change in the morphology of the polymer. Increased polymer concentration may have provided the matrix with higher tortuosity and poor water porosity for diffusion of drug. Moreover, higher polymer concentration would have resulted in viscous environment of the system inhibiting movement of water into the matrix for easy diffusion of the drug into the surroundings [21] *In vitro* release of drug also depends on nature of plasticizer. As the concentration of hydrophilic plasticizer was increased the release of drug was also found to be increased, as shown in [Figure 2]. It may be due to quick absorption of water by formation of large number of hydrogen bonds and helped in faster diffusion of drug from system. From *in vitro* drug release study, it was found that F3 showed maximum release (88.59 ± 2.74) at the end of 30 min which was the prerequisite for the achievement of therapeutic action. However formulations F1 and F2 containing lower concentration of Chitosan showed more release compared to F3 at the end of 30 min, but tensile strength was lesser than F3.

Stability studies

Optimized formulation did not show any physical changes during the study period and also exhibit excellent drug content over the storage period.

In Vivo Study:
Place of Study – M A Rangoonwala Dental College, Pune.
Study Period – 1 year 6 months
Study Population – Study consists of two groups, 30 patients included in each group. Patients diagnosed with oral submucous fibrosis.
Group I – (30 patient) treated with conventional intralesional injection of dexamethasone 4mg/ml with normal syringe once week for 6 consecutive weeks.
Group II – (30 patient) treated with sustained release dexamethasone mucosal patch with dexamethasone 2mg patch bilaterally on mucosa once /week for 6 weeks.
Sample size – 60

Methodology for in vivo study:
- All the patients were subjected to thorough case history and clinical examination. Following parameters were included in the establishment of diagnosis and following two parameters were satisfied for inclusion in the study.
- Restricted mouth opening and changes in oral mucosa including presence of palpable vertical bands, stiffness and blanching.
- Difficulty in chewing.
- Ulceration in the oral cavity.
- Burning sensation on eating spicy food.

Following establishment of diagnosis, each patient were informed about the condition, its precancerous potential and advised to discontinue use of areca nut in all forms. A detailed case history including habit of history with details of duration, in years, frequency of chews per day.

A clinical examination of the oral cavity was carried out under artificial light which includes extra oral examination and intra oral examination.

On extra oral examination, the patient's mouth opening was measured with reference to the interincisal points with mouth opening being maximum, using divider and metallic scale.

On intra oral examination findings such as blanching of oral mucosa, presence of vesicles and ulcers, presence of palpable band, limitation of tongue movement.

All patients' were undergone oral prophylaxis (scaling and polishing) to removes extrinsic stains in order to motivate the patient towards recovery and was inform the investigator patient if patient resumes habit. All patients were advised complete haemogram.

Patients were evaluated every week during treatment period. A clinical examination was carried out at each recall visit and findings was compared with those at the beginning of treatment. Mouth opening assessed once before the beginning of the treatment and once at the end of the treatment regime. [18,19]

SELECTION CRITERIA
INCLUSION CRITERIA
1) Changes in the oral mucous membrane that includes the presence of palpable vertical fibrous band, blanching of the oral mucosa with burning sensation and/or ulceration.
2) Patient must belong to the Grade I and Grade II category of oral sub mucous fibrosis.
3) Patient must be above 18 years and below 60 years.
4) Changes in the oral mucous membrane that includes the presence of palpable vertical fibrous band, blanching of the oral mucosa with burning sensation and/or ulceration.
5) Positive history of chewing areca nut with tobacco, burning sensation on eating spicy foods and restricted mouth opening.

EXCLUSION CRITERIA
1. Patients suffering from systemic disorder which prevent administration of corticosteroids
2. Patient age not below 18 and above 60 years.
3. Patients who are not willing to take medications for the treatment of oral Sub mucous fibrosis.
4. Patient having advanced oral sub mucous fibrosis, where mouth opening is

Severely reduced and surgical intervention is required for treatment.
Patient who do not withdraw the habit.

RESULTS AND DISCUSSION

Calibration of Dexamethasone by UV Spectrophotometer

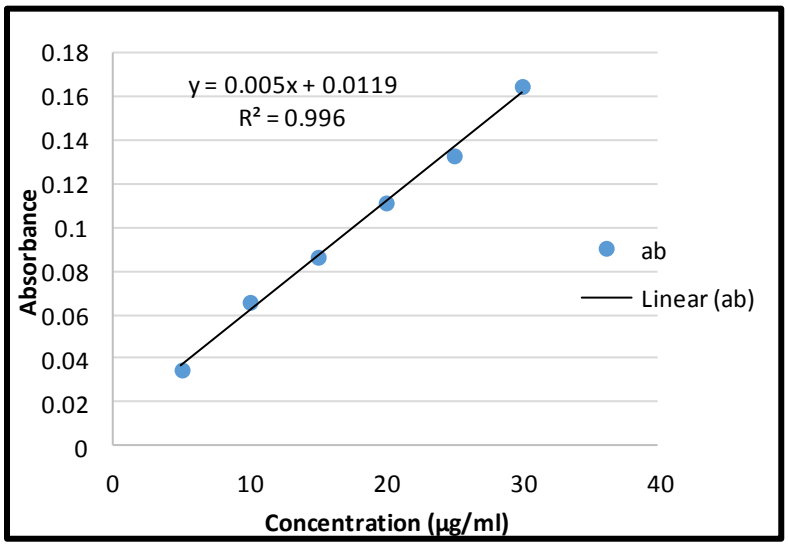


Figure 3: Calibration curve of Dexamethasone.

Preformulation studies

Organoleptic properties: Drug powder was white in colour and found odorless.
Description: It was found to be amorphous powder.
Melting point: The melting point of Dexamathasone was found to be 261°C (Standard = 262°C to 264°C)
Solubility: Insoluble in water, slightly soluble in organic solvents such as methanol, acetone, DMSO.

Evaluation of Dexamethasone buccal patch of optimized batch

Table 4: Evaluation of dexamethasone buccal patch (optimized).

Formulation code	Visual appearance	Thickness	Weight variation	Surface pH
F1	Transparent	0.40	177	6.1
F2	Transparent	0.40	210	6.2
F3	Semi-Transparent	0.41	200	6.2
F4	Transparent	0.42	200	6.5
F5	Non-Transparent	0.40	210	6.5
F6	Semi-Transparent	0.41	180	6.4
F7	Semi-Transparent	0.42	208	6.3
F8	Non-Transparent	0.45	208	6.1
F9	Non-Transparent	0.44	210	6.2

Table 5: Evaluation parameters of optimized batch of Dexamethasone buccal patch.

Formulation code	Folding endurance	Drug content	Mucoadhesive time (in minutes)
F1	72	66.30	80
F2	78	66.85	110
F3	75	60.55	114
F4	78	63.35	96
F5	70	64.55	106
F6	76	62.75	115
F7	80	59.25	90
F8	78	59.35	112
F9	73	60.60	105

In vitro diffusion study

Table 6: data for cumulative % drug release.

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
30	3.61	3.42	4.72	3.42	3.07	4.00	7.41	3.00	3.55
60	7.09	10.83	11.25	7.42	8.69	7.07	13.94	7.23	8.15
90	13.62	20.05	18.66	12.14	15.22	12.4	23.16	11.96	13.82
120	21.87	26.58	25.81	18.67	22.63	16.23	30.07	17.61	18.63
150	30.42	34.3	35.08	26.29	31.85	22.48	31.89	23.09	25.68
180	40.22	42.85	45.18	35.06	39.57	29.7	34.96	30.00	33.93
210	49.77	52.65	55.79	45.16	48.07	37.68	42.68	37.61	43.48
240	60.04	64.53	62.74	55.94	57.25	46.45	51.18	46.27	53.75

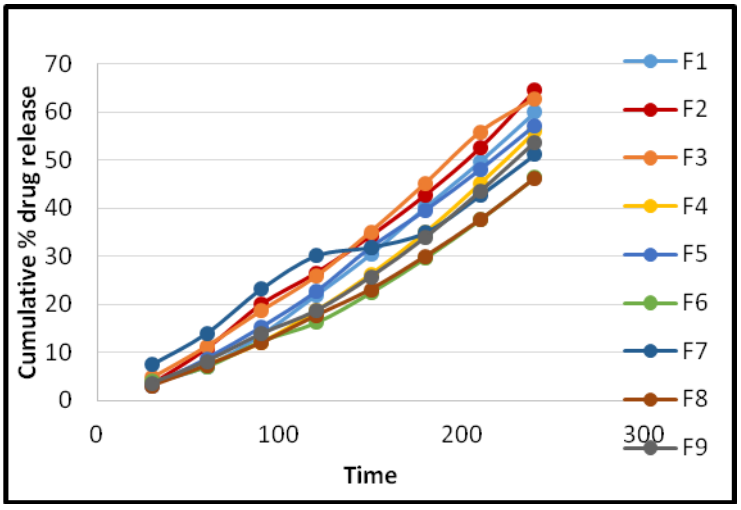


Figure 4: Cumulative % drug release from all batches.

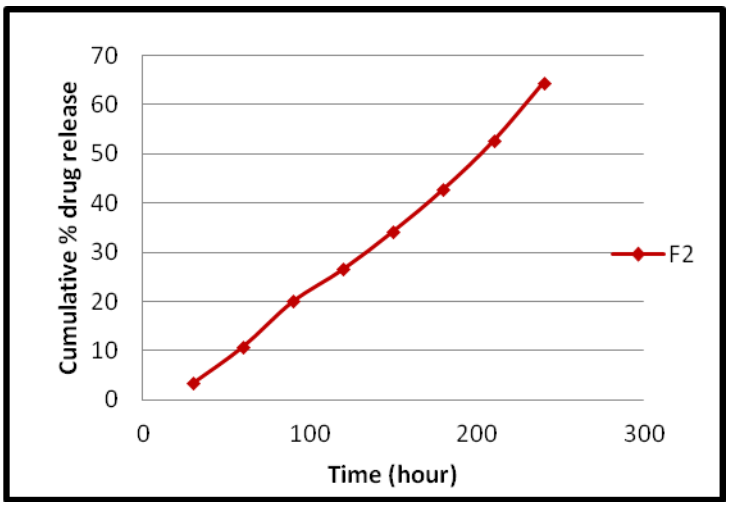


Figure 5: Cumulative % drug release from optimized batch (F2).

Ex-vivo permeation release study

Table 7: Ex-vivo permeation study.

Time (min)	F2
30	3.76
60	6.86
90	12.63
120	20.25
150	29.83
180	39.93
210	50.71
240	61.33

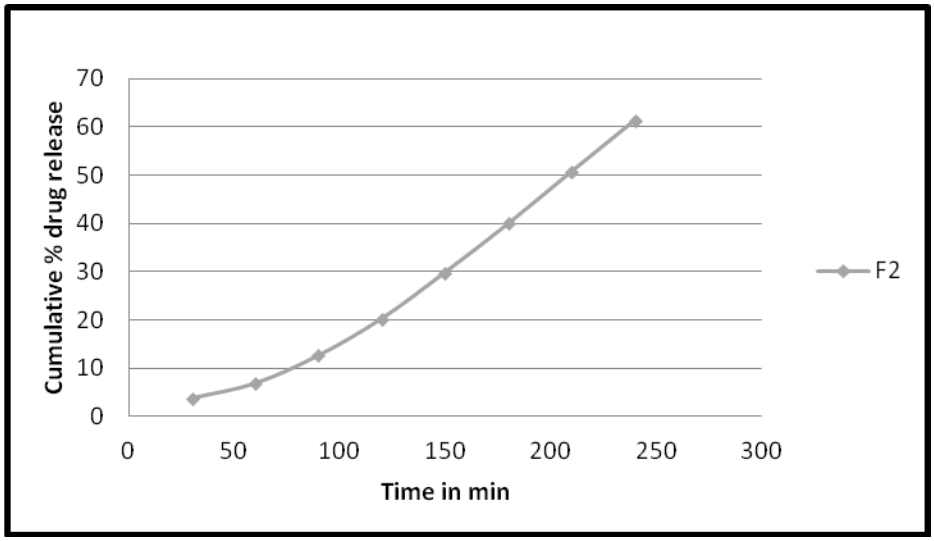


Figure 6: Cumulative % drug release from optimized batch (F2).

Stability studies

Table 8: Stability testing at 40±2˚C and RH 75±5% (optimized).

Formulation	Parameter	Initial	40˚C/ 75% RH 7 days	40˚C/ 75% RH 14 days
F2	Drug content (%)	66.85%	66.25%	66.05%

FTIR study

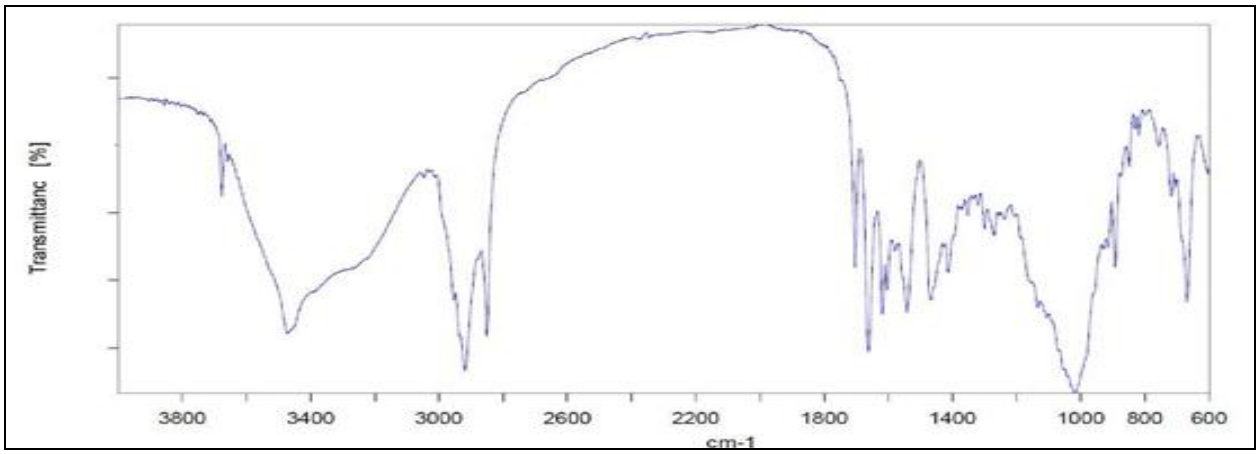


Figure 7: FTIR spectrum of Dexamethasone drug.

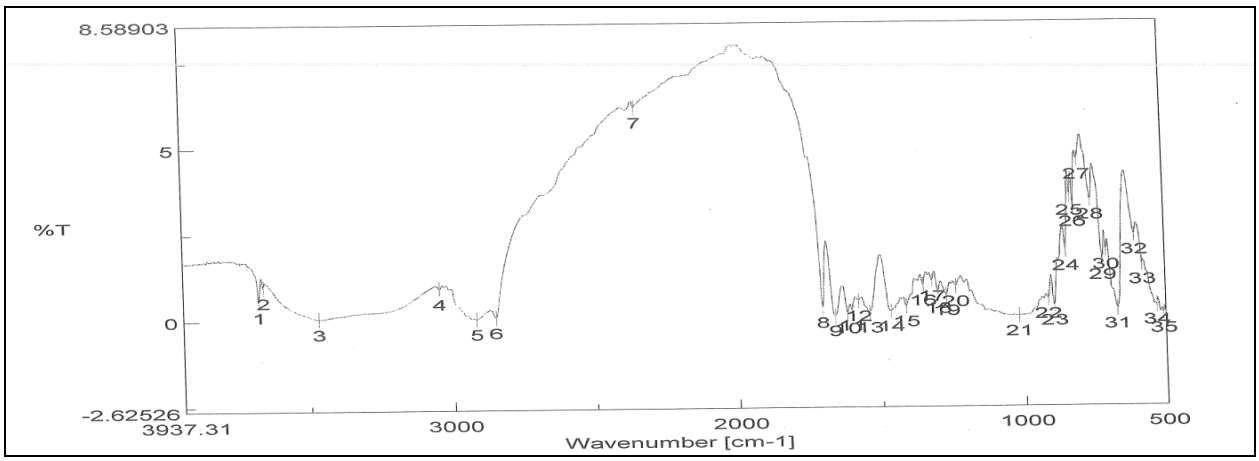


Figure 8: FTIR spectrum of Dexamethasone + Polyethylene glycol 400.

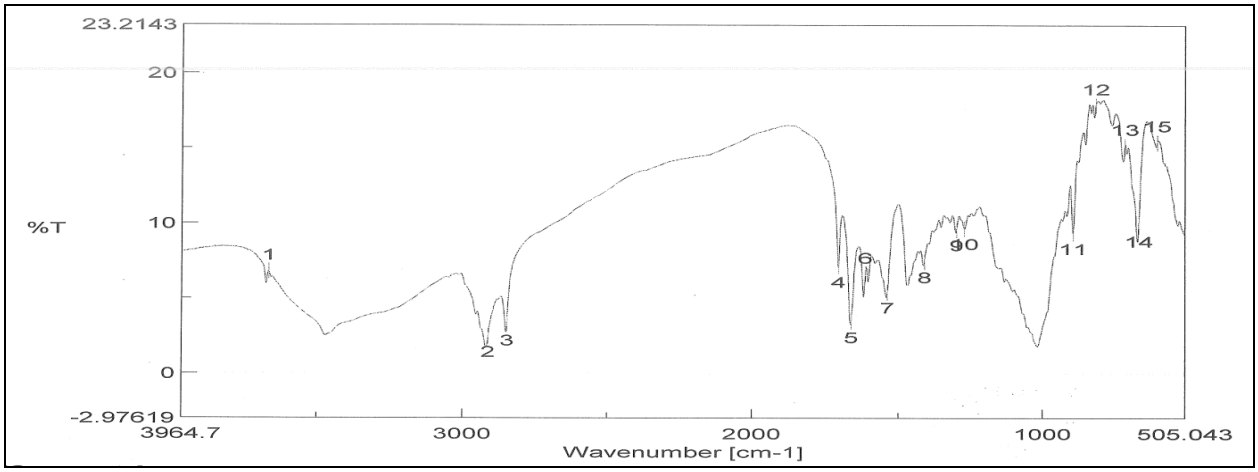


Figure 9: FTIR spectrum of Dexamethasone + Chitosan.

XRD study (X-ray Diffraction)

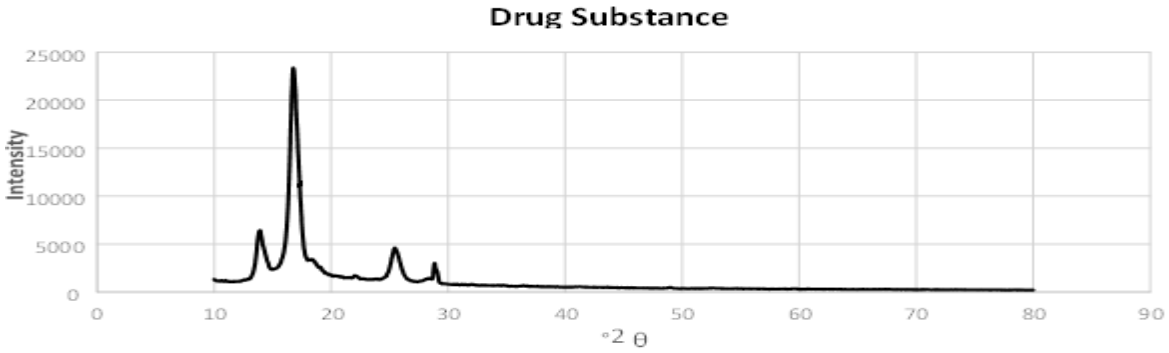


Figure 8: pXRD of Dexamethasone.

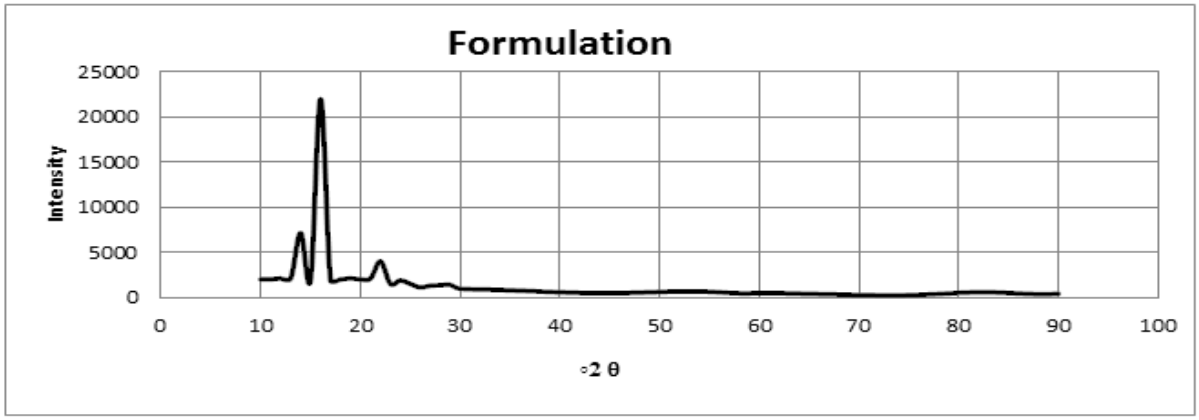
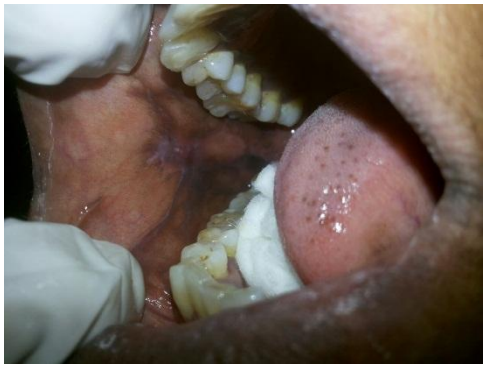
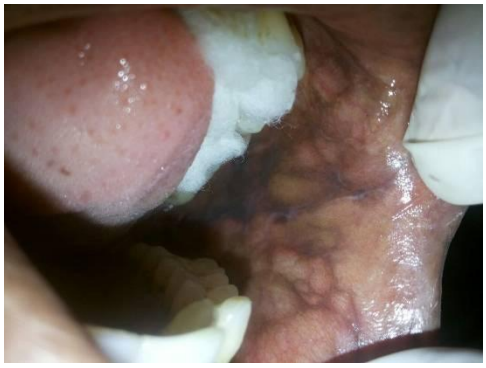


Figure 9: pXRD of optimized formulation.





Result of Clinical study:

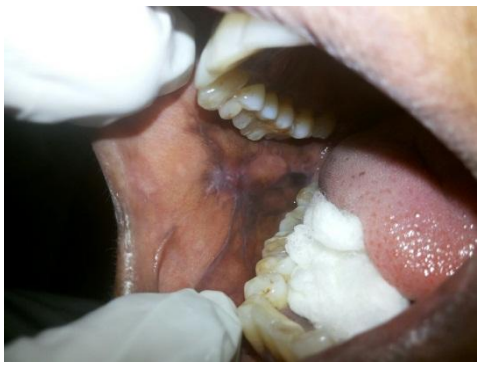
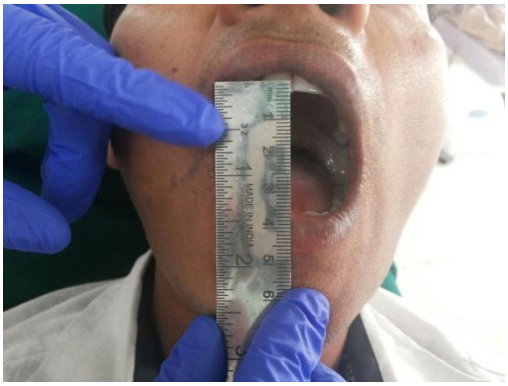


Figure7: Before Application Buccal patch-limited Mouth opening



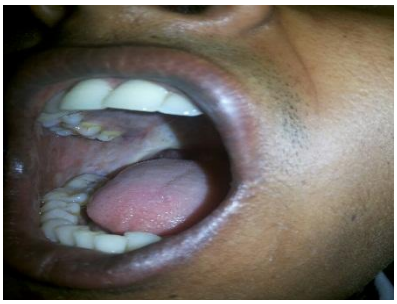


Figure. 8. Recovery after Application of Buccal Patch.

CONCLUSION

Oral submucous fibrosis (OSMF) is a chronic debilitating disease of the oral cavity characterized by inflammation and progressive fibrosis of the lamina propria and submucosa, that results in marked rigidity and eventually inability to open the mouth. The objective of the present study was to develop mucoadhesive buccal patch of Dexamethasone for the treatment of oral submucous fibrosis. In formulation, chitosan is used as a polymer and PEG 400 as a plasticizer. Backing membrane was prepared by using ethyl cellulose and isopropyl alcohol. The solvent casting method was used for the preparation of mucoadhesive buccal patch as it is cost effective and efficient method. Preformulation studies of Dexamethasone were carried out. FTIR studies implied that there were no interactions between drug and polymers. The prepared batches were evaluated for visual appearance, thickness, folding endurance, weight variation, swelling index, surface pH, mucoadhesive time, % drug content, in-vitro diffusion and ex-vivo permeation study. Total nine batches of Dexamethasone mucoadhesive buccal patch were prepared successfully using chitosan as a polymer and PEG 400 as a plasticizer by solvent casting method. Based on results batch F2 was selected as optimized formulation. From invitro release of batches, F2 was found best, showing release of drug 64.53% in 4 hours.

A clinical examination of the oral cavity was carried out under artificial light which includes extra oral examination and intra oral examination. The results of the present study of mucoadhesive semi-solid drug design for the treatment of OSMF will be useful for drug industry for the benefit of patients suffering from OSMF. The most important advantage of the Mucoadhesive buccal films is that it contains a lower drug dose, adequate for therapeutic effect as it is placed directly on the site of the inflammation, when compared to conventional administration. Moreover, this Mucoadhesive buccal patch is very convenient because it is non-irritant and self-administration is possible. Given promising therapeutic effects, the buccal film developed here could become a local drug delivery device for management of oral submucous fibrosis, ulceration and lichen planus.

ACKNOWLEDGEMENT

The authors would like to thank the Management Dr Vishwanath Karad MITWPU, School of Pharmacy,, Pune, (Formerly MAEER's, Management, Principal Maharashtra Institute of Pharmacy, Pune-India) for providing laboratory facilities and supporting this research work. Also author would like to thanks to management and staff of M.A. Rangoonwala College of Dental Sciences & Research center, Pune for Clinical study.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest in publication of this paper.

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