IJMPR 2021, 5(4), 282-286

International Journal of Modern Pharmaceutical Research

www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Research Article

SJIF Impact Factor: 5.273

FORMULATION AND EVALUATION OF ORAL MUCOADHESIVE BUCCALFILM OF CEPHALEXIN

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Received on: 24/06/2021

Revised on: 14/07/2021

Accepted on: 04/08/2021

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ABSTRACT

The aim of this work was to develop and evaluate a buccal films for oral delivery of Cephalexin. **Method:** Cephalexin-loaded buccal films were prepared by using mucoadhesive polymers like HPMC K_4M and Chitosan, using a solvent casting method. The films were evaluated in terms of thickness, weight, folding endurance, drug content, drug release study, release kinetics studies, and short-term stability study. **Results:** The cumulative percentage release of Cephalexin from different mucoadhesive buccal films varied from 96.68±1.53 % to 99.89±1.21 % depending uponthe polymer plasticizer ratio and the type of plasticizers used. Theorder of *in-vitro* drug release data was found to be highest for formulation F11 [(containing Chitosan: tween80: PEG 400 (10%)]. The drug release kinetic showed Higuchi release kinetic and found to follow non-Fickian release mechanism. Stability results exhibited no significant change in drug content, and percentage drug release when stored at room temperature. **Conclusion:** It can be concluded that buccal films of Cephalexin could provide sustained buccal delivery for prolonged period.

KEYWORDS: Cephalexin, Buccal film, HPMC K_4M, Chitosan, plasticizers.

1. INTRODUCTION

An ideal drug delivery system should deliver specified quantity of therapeutic agent and should maintain therapeutic level of drug for a specified duration at the appropriate site in the body.[1] Therefore, a drug delivery system should supply drug at a mandatory rate over a specified period of treatment. The two distinct features of drug delivery are spatial delivery and temporal or timed delivery of a drug.[2] Targeting and delivering a drug to a particular tissue or organ is called spatial delivery, while temporal or timed delivery represents controlling the rate of drug delivery to the target tissue.[3] A properly designed controlled release drug delivery system only can deliver a therapeutic agent at a pre-programmed rate.[4] Conventional oral formulations provide adequate safety to the patientsby balancing the pharmacokinetic and pharmacodynamic profile of drugs and thereby provide clinically effective therapy.[5] Oral route of drug administration possesses several advantages based on the drug incorporated.[6] The advantages are patient acceptability, comfort of administration and lesser cost of formulation and therapy.[7] Oral route of drug delivery also has some disadvantages such as; variation in rate of drug absorption, irritation of gastro intestinal tract (GIT) mucosa and high rate of first pass metabolism.[8] This route of administration needs high amount of dose required to produce therapeutic effect and otherunwanted effects due to intestinal motility, mucosal barrier and presence of food.[9] The GIT is the major route of drug delivery to the systemic circulation.[10]

2. MATERIALS AND METHODOLOGY

Cephalexin and Chitosan were purchased from Yarrow Chem. products, Mumbai, India. Glycerine and Methanol were purchased from HI media laboratories Pvt. Ltd. Poly ethylene glycol 400, Potassium dihydrogen phosphate and Sodium hydroxide Were purchased from S.D. Fine Chem. Ltd, Mumbai, India. Hydroxypropyl methylcellulose was purchased from Techno Scientific Products, Bengaluru.

3. Experimental Methods

3.1 Melting Point determination

Melting point of Cephalexin was determined by capillary fusion method. The melting point of the sample was found to be 326.2^{o}C ±0.5^{o}C and which was similar with previously reported value (326^{o}C -328.2^{o}C) indicated that the drug sample was pure.

3.2 Determination of Solubility

Solubility study of Cephalexin was determined for selection of diffusion medium in different solvents at room temperature. The volume of solvent required to dissolve the drug was recorded in Table No. 01. The solubility study revealed that the drug sample issoluble in water, and pH 6.8 phosphate buffer and insoluble in methanol and ether.

Table 01: Solubility studies of Pure Cephalexin in different Solvents.

Sl. No	Solvent	Solubility(mg/ml)	Observation
1	Distilled water	21.20±0.23	Soluble
2	Methanol	0.93±0.011	Insoluble
3	Phosphate buffer pH6.8	28.11±0.047	Soluble
4	Ether	0.85±0.032	Insoluble

3.3 Compatibility study using FT-IR

The IR spectra of Cephalexin alone and its physical mixtures with HPMC K_4M, Chitosan, tween 80, glycerin and PEG 400 were recorded in order to determine the physicochemical compatibility between drug and excipients used in the formulation. Compatibility study was carried out by using Fourier spectrophotometer to get FTIR spectrum. FTIR spectrum so obtained deals about characteristic of entire molecule and provides structural information by referring to peaks associated with characteristics groups. The major observed IR peaks in cephalexin were 3269.19 cm^{-1} (3100-3500) (N-H), 1688.70 cm^{-1} (1680-1760) (C=O), 1163.78 cm^{-1} (1020-1220) (C-N), and 1278.85 cm^{-1} (1000-1300) (C-O). Cephalexin showed its characteristics peaks with excipients physical mixture. Presence of all characteristics peak of Cephalexin in its physical mixture indicated that there was no interaction between the drug and excipients. Hence, polymers and permeation enhancers used for the preparation of buccal films showed compability with drug. All the characteristic peaks exhibited by Cephalexin is shown in Table No. 02 and Figure No. 01 and 02.

Table 02: Results of FTIR spectrum.

Functionalgroup	Observed peaks cm^{-1}			
	Cephalexin	Drug: Chitosan mixture	Drug: HPMC K4M mixture	Optimized formulation
(N-H) (s)	3269.19	3219.19	3215.81	3360.19
(C=O) (s)	1688.70	1688.87	1641.73	1643.70
(C-N) (s)	1163.78	1168.04	1153.42	1154.25
(C-O) (s)	1278.85	1278.86	1244.45	1221.59

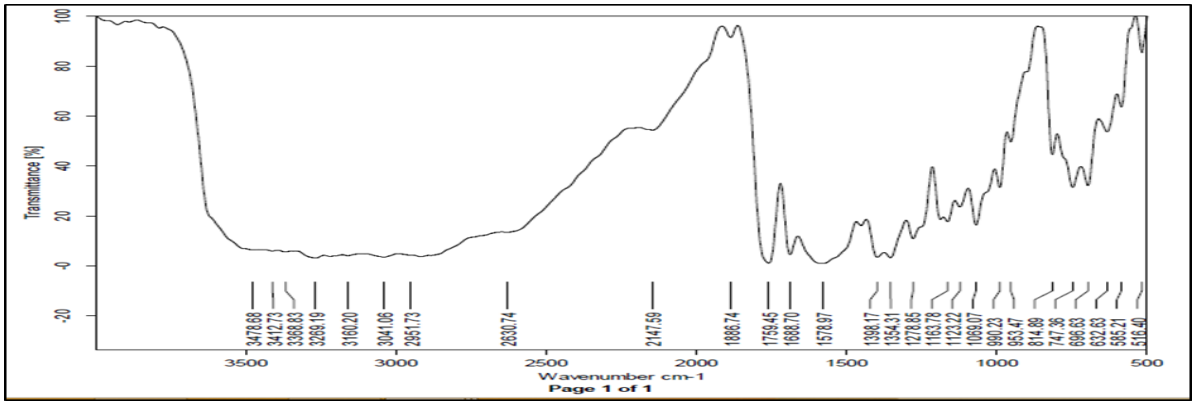

Figure 01: FTIR spectrum of pure Cephalexin

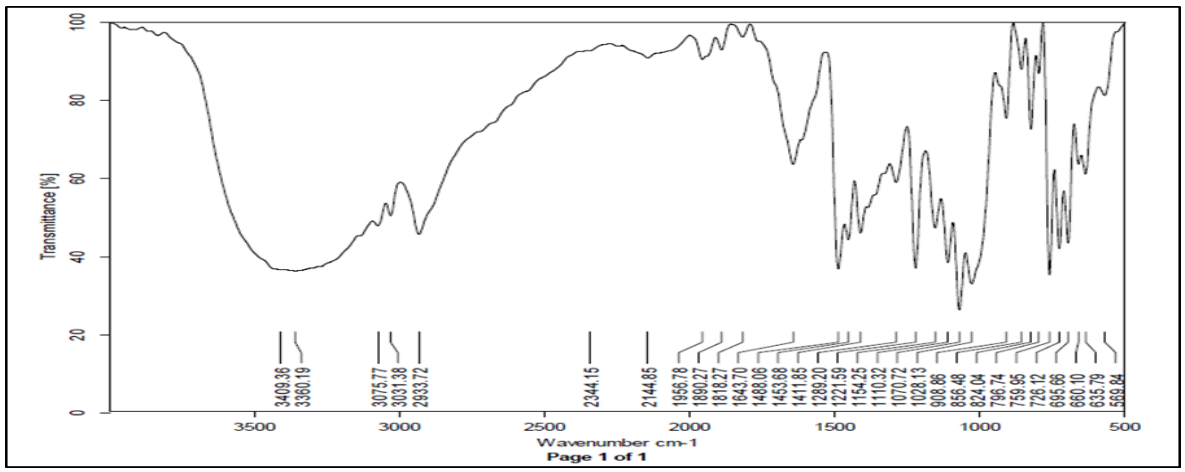

Figure 02: FTIR spectrum of optimized formulation.

Preparation of buccal film of Cephalexin

In the present study, buccal film containing Cephalexin was prepared by solvent casting method using different polymers i.e., hydroxyl propyl methyl cellulose (HPMC K4M) and chitosan. Polymers were accurately weighed and dissolved in 10 ml of water: ethanol (1: 1) solution and kept aside to form clear solution. The resulting polymer solution was plasticized using plasticizer (glycerine and poly ethylene glycol). 10 ml ofthe above solution was added with calculated amount of Cephalexin. This solution wassonicated for 15 min and kept overnight to remove air bubbles and poured in to a glass mould having a surface area of 40 cm^2. It was dried in room temperature andthe dried film were cut into 2×2 cm and wrapped in aluminium foil and kept in a desiccator. The composition of the film is given in Table No. 03.

Table 0*3*: Composition of different mucoadhesive buccal films containing cephalexin.

Formulation code	Drug			Enhancer			Solvent
	Cephalexin (mg)	HPMC K4M	Chitosan(mg)	Tween 80w/v (%)	Glycerin w / v (%)	PEG 400 w/v(%	Water: Ethanol
F1	100	200	--	05	--	05	10
F2	100	300	--	05	--	05	10
F3	100	200	--	05	05	-	10
F4	100	300	--	05	05	-	10
F5	100	--	200	05	--	05	10
F6	100	--	300	05	--	05	10
F7	100	--	200	05	05	-	10
F8	100	--	300	05	05	-	10
F9	100	200	--	05	--	10	10
F10	100	200	--	05	10	-	10
F11	100	--	200	05	--	10	10
F12	100	--	200	05	10	-	10

Evaluation of mucoadhesive buccal films

The prepared buccal films were evaluated to study the effect of type of release retardant polymer, concentration of polymers, and concentration of plasticizers on the *in-vitro* release profile of drug and on the physical characteristics of the film. Prepared films were evaluated for their physical appearance,thickness uniformity, weight uniformity, drug content uniformity, moisture content, percentage moisture uptake, folding endurance, tensile strength, *in-vitro* drug release, release kinetics study and short-term stability study.

Physical Appearance

All the films were evaluated for their physical appearance, and they were found to be flexible, uniform, smooth, transparent, non-sticky, and homogeneous in nature.

Film thickness

The thickness of the films varied from 0.021 ± 0.0053 mm to 0.029 ± 0.0031 mm. Low standard deviation values in the film thickness measurements ensured uniformity of the films which further indicated the reproducibility of the procedure followed for the preparation of the films. Result of film thickness is shown in Table No. 04.

Weight uniformity

The weight of the prepared buccal films ranged from 26.71±0.21 mg and 31.40±0.11 mg, all the films showed low standard deviation values. A result of weight uniformity is shown in Table No. 04.

Drug content uniformity

Drug content was determined at 257 nm using UV-spectrophotometer-1800. The results of content uniformity indicated that the drug was uniformly dispersed. The content was in range of 96.32%±1.46 to 99.22 %±0.85. Thissuggests that the process employed in the preparation of the films was capable of affording uniform drug contentand minimum variability. Results of drug content estimation is shown in Table No. 04.

Moisture content estimation

The moisture content found in the range of 2.54±0.052% to 3.21±0.042%. The moisture content increases with increase in concentration of plasticizer. The moisture content was higher for formulation F9, F10, F12. The lowermoisture content in the formulations helps them to remain stable and become a completely dried and brittle film. Result of moisture content estimation is shown in Table No. 04.

Percentage moisture uptake

The moisture uptake in the films ranged from 3.64±0.031

to 5.19±0.027%. The moisture uptake was found to be higher in batches F9, F10 and F12. Again, low moisture uptake protects the material from microbial contamination and bulkiness. Result of percentage moisture uptake estimation is shown in Table No. 04.

Folding Endurance

Folding endurance values varied between 257.0±2.41 and 294.7± 2.73. The folding endurance values >250 revealed that the prepared patches were having the capability towithstand the mechanical pressure along with goodflexibility.

Tensile Strength

The tensile strength of buccal films, prepared with HPMC K_4M and Glycerin was found in the range of 0.52±0.018 kg/cm^2 to 0.71±0.042 kg/cm^2.

Table 04: Physical characterization data for the mucoadhesive buccal film.

Formulation	Film thickness* (mm)	Weight uniformity*(mg)	Drug content* (%)	Moisture content* (%)	Moisture uptake*(%)	Folding Endurance*	Tensile Strength *kg/cm^2
F1	0.021±0.0053	30.51±0.24	97.32±1.23	2.85±0.021	3.85±0.042	764.5±2.40	0.58±0.026
F2	0.027±0.0021	26.71±0.21	96.32±1.46	2.88±0.048	3.97±0.025	257.0±2.41	0.63±0.010
F3	0.025±0.0055	28.41±0.43	98.91±0.92	2.91±0.072	3.90±0.027	283.3±2.70	0.65±0.019
F4	0.023±0.0012	30.44±0.29	98.90±1.42	2.80±0.019	3.78±0.024	279.2±2.39	0.59±0.012
F5	0.024±0.0036	29.41±0.26	98.78±0.59	2.70±0.010	4.83±0.027	294.7±2.73	0.60±0.024
F6	0.028±0.0020	28.30±0.85	98.22±0.36	2.76±0.018	3.88±0.016	290.0±2.74	0.64±0.035
F7	0.029±0.0031	26.98±0.32	97.76±0.55	2.58±0.037	4.22±0.029	264.6±2.11	0.52±0.018
F8	0.022±0.0072	31.40±0.11	98.98±1.84	2.54±0.013	3.64±0.041	278.2±2.64	0.62±0.065
F9	0.027±0.0044	29.48±0.84	96.91±0.47	3.14±0.018	5.10±0.051	276.4±2.42	0.57±0.053
F10	0.025±0.0039	28.13±0.72	98.11±1.06	3.19±0.032	4.97±0.024	289.7±2.44	0.56±0.092
F11	0.024±0.0018	30.70±0.69	99.22±0.85	2.86±0.018	4.12±0.029	279.6±1.90	0.61±0.063
F12	0.024±0.0021	29.79±0.28	98.19±1.25	3.21±0.042	5.19±0.027	289.5±2.66	0.54±0.054

***In-vitro* drug release studies**

The *in-vitro* release profiles of Cephalexin from Cephalexin buccal films are shown in Table No. 05. The cumulative percentage release of Cephalexin from different mucoadhesive buccal films varied from 96.68±1.53% to 99.89±1.21% depending upon the polymer plasticizer ratio and the type of plasticizers used.

The *in-vitro* drug release data was found to be highest for formulation F11(99.89±1.21) [(containing Chitosan: tween80: PEG 400 (10%)]. The results indicated that the release of drug from films decreaseswith increasing concentration of plasticizer. The cumulative percent of drug release in 24 hour was noted. The drug release was found to increase with the use of hydrophilic polymer in the polymer matrix. This is due to the fact that dissolution of an aqueous soluble fraction of the polymer matrix leads to the formation of gelataneous pores.

The formulation of such pores leads to decreasing mean diffusion path length of drug molecules to release into the diffusion medium and hence, to cause higher release rate. Formulation F11 showed highest percentage of drug release at the end of 24 hours. Result of *in-vitro* drug release study is showed in Table No. 07 Figure No. 07.

Stability Studies

Based on the results of *in-vitro* drug release behaviour, formulation F11 was considered as optimized formulation. The stability studies were carried out at room temperature, for a period of 3 months. Cephalexin buccal film was analysed for % drug content, tensile strength, folding endurance and *in-vitro* drug release behaviour. The results of stability studies are given in the Table No. 06. Results fromthe stability studies shown that there was no changein the % drug content, tensile strength, folding endurance and % CDR of the prepared buccal film. Hence prepared Cephalexin buccal film formulation was physicochemically stable throughtout study period.

Table 05: Stability studies of optimised formulation F11.

Sl. No.	Parameter	Results obtained on1st day	Results obtained after30 days
01	**Drug content (%)**	99.22±0.85	99.20±0.74
02	**Tensile strength (kg/cm^2)**	0.61±0.063	0.59±0.019
03	**Folding endurance**	279.6±1.90	277.8±1.90
04	**% CDR**	99.89±1.21	99.83±1.08

Table 06: Table showing percentage drug released during 24 hours.

Cumulative percentage drug release												
Time	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
0.5	12.55±1.31	9.89±0.54	15.43±1.22	12.55±1.26	19.53±1.35	11.29±1.33	17.50±1.26	10.27±1.1	9.45±1.52	8.59±1.57	8.05±1.39	10.57±1.30
1	35.52±1.83	22.02±0.22	32.50±1.90	28.52±1.81	36.77±1.78	20.51±1.87	23.18±1.21	18.50±1.74	17.22±1.81	15.44±1.89	12.52±1.83	16.77±1.38
2	52.61±1.86	36.93±1.89	46.60±1.21	43.61±1.92	50.84±1.33	36.61±1.43	38.61±1.22	32.64±1.89	30.68±1.84	28.61±1.86	27.44±1.87	32.60±1.90
4	68.31±1.43	47.31±1.23	57.46±1.25	51.31±1.33	68.91±1.49	49.31±1.40	51.30±1.47	48.30±1.99	44.32±1.41	45.31±1.43	38.36±1.41	47.31±1.43
6	84.58±1.56	62.08±1.62	72.58±1.51	65.50±1.37	78.50±1.46	68.88±1.82	71.44±1.56	65.50±1.86	56.54±1.50	59.58±1.56	57.44±1.49	62.58±1.56
8	99.51±2.04	74.50±1.09	84.51±2.77	78.51±2.73	89.51±1.45	79.51±1.58	80.50±1.12	77.51±1.95	68.58±1.44	70.51±2.04	69.22±2.83	74.51±2.04
12		88.99±1.59	98.68±1.72	86.64±1.35	99.29±1.20	92.55±1.42	91.68±1.50	85.50±1.73	77.99±1.54	82.68±1.59	84.78±1.45	86.68±1.59
18		99.21±1.63		98.76±1.44		99.06±1.24	99.22±1.59	97.51±1.95	86.29±1.45	88.68±1.59	92.77±1.22	98.68±1.59
24									97.99±1.73	96.68±1.53	99.89±1.21	

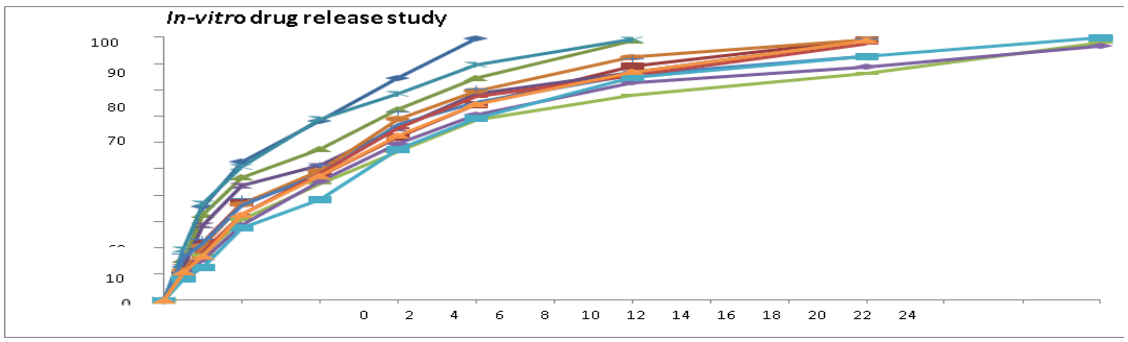

Figure 03: Comparative *in-vitro* drug release profile of Cephalexin buccal film (F1-F12).

CONCLUSION

Buccal drug delivery systems offer a promising route for drug delivery not only to the buccal mucosa for the treatment of oral conditions but also for systemic delivery by absorption through the mucosa to the systemic circulation at a predetermined and controlled rate. Absorption of therapeutic agents from the oral mucosa overcomes premature drug degradation due to enzyme activity and pH of the gastrointestinal tract,avoids active drug loss due to first-pass hepatic metabolism and thus improves systemic bioavailability. In addition, the buccal mucosa permits a prolonged retention of a dosage form especially with the use of mucoadhesive polymers without much interference in activities such as speech or mastication unlike the sublingual route. In order to improve the efficacy and to minimize the side effects associated with oral administration, mucoadhesive buccal films of Cephalexin using HPMC K_4M and Chitosan were prepared by solvent casting technique.

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