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FORMULATION AND EVALUATION OF BUPRENORPHINE BUCCAL TABLETS

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Abstract:

Buccal tablet of oral formulations of these drugs have been developed to improve their acceptability to patients and thus improve compliance. The focus of present investigation was to improve solubility, bioavailability and to achieved rapid onset action. Buccal tablets of Buprenorphine were prepared by direct compression technique. Four Formulations were formulated using Ethyl cellulose and HPMC as polymers on Swelling index, Disintegration time. In addition, the prepared tablets were also evaluated for weight variation, thickness, moisture absorption, friability, content uniformity, wetting time and drug release studies. Formulation reveals fast dissolution and disintegration rate of optimized Buprenorphine buccal tablets.

Key words: *Buprenorphine, Direct compression technique, FTIR studies, Synthetic polymers polymers, Drug release studies.*

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INTRODUCTION:

Buccal route of drug delivery is a good alternative, amongst the various routes of drug delivery. Buccal drug delivery is most advantageous because it abundant blood supply in buccal mucosa, bypassing the hepatic first pass effect and accessibility [1]. Buccal route of drug delivery provides the direct access to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading to high bioavailability. [2] Tablets have been the most commonly investigated dosage form for buccal drug delivery to date. Buccal tablets are small, flat and oval with a diameter of approximately 5–8 mm. [3] Unlike conventional tablets, buccal mucoadhesive tablets allow for drinking and speaking without major discomfort. They soften, adhere to the mucosa, and are retained in position until dissolution and/or release is complete. [4] These tablets can be applied to different sites in the oral cavity, including the palate, the mucosa lining the cheek as well as between the lip and the gum. Successive tablets can be applied to alternate sides of the mouth. [5] The major drawback of buccal bio adhesive tablets is their lack of physical flexibility, leading to poor patient compliance for long-term and repeated dose. Bio adhesive tablets are usually prepared by direct compression, but wet granulation techniques can also be used. [6] Buprenorphine has to be released in a sustained manner, so that therapeutic concentration can be maintained. To formulate and evaluate Buprenorphine buccal tablets.

MATERIALS:

Buprenorphine was collected as a gift sample from Hetero laboratories, Hyderabad, Synthetic polymers, super disintegrants and other excipients were purchased from Synpharma Research Labs, HYD.

METHODODOLOGY:

Formulation development

Table-1: Formulation table

S.NO.	INGREDIENTS	F1	F2	F3	F4
1	Buprenorphine	5	5	5	5
2	Ethyl cellulose	25	50	-	-
3	HPMC	-	-	25	50
4	Lactose	53	28	53	28
5	Aspartame	2	2	2	2
6	Microcrystalline Cellulose	10	10	10	10
7	Magnesium stearate	3	3	3	3
8	Talc	2	2	2	2
9	Total Wt	100	100	100	100

Preparation method:

Buccal tablet formulations of Buprenorphine were prepared by direct compression method. Two different grades of HPMC and Ethyl cellulose were used as release retardant materials. Magnesium stearate and talc were used as lubricant/glidants. Sufficient quantities of microcrystalline cellulose were used to raise the total bulk of the tablets to a weight of 100 mg each. All the ingredients were passed through sieve # 80 before mixing. Initially drug and polymers were mixed thoroughly and then required quantities of fillers were added and finally the blend was mixed with talc thoroughly for 5 min in a poly bag and then required amount of magnesium stearate was added and mixed for another 5min. Powder blends of all the above formulations were compressed on single punch tablet press using 8mm punches to the hardness of 6Kg/cm^2. [7,8]

FT-IR study [9]

Compatibility studies of Apomorphine and the disintegrants were carried out by using Fourier Transform Infrared Spectroscopy (FTIR). Fourier transform infrared spectra of the samples were obtained in the range of 4000 to 450 cm-1 using a FTIR by the KBr disc method.

Evaluation parameters [10.11,12,13]:

Drug content:
Ten tablets were weighed and powdered in a mortar. Accurately weighed tablet powder samples equivalent to 20mg of Buprenorphine was transferred to a 100mL volumetric flask, and the Buprenorphine was extracted into 75mL methanol and then finally the volume was made to 100 mL with methanol. This solution was suitably diluted with 6.8 phosphate buffer and the absorbance was measured at 269 nm. The estimations were carried out in triplicate.

Uniformity of weight of tablets:
The individual and total weight of 20 tablets from each batch was determined. Percentage deviation of the individual weights from the average weights was calculated.

Hardness:
The hardness of the tablets was measured with a Pfizer hardness tester. The results reported were average of 6 tablets for each formulation.

Friability:
For each formulation 10 tablets were weighed, placed in Friabilator and were subjected to 100 rotations in 4min. The tablets were reweighed and friability was calculated by the following formula:
Friability=W_2-W_1/W_1

Moisture absorption studies:
Agar at 5% w/v was dissolved in hot water and then transferred to a petri dish and was allowed to be solidified. Prior to the study, six tablets were placed in a vacuum overnight to remove moisture. They were weighed initially and then positioned on the top of the agar and incubated at 37 ºC for one hour. At the end of the test, the tablets were reweighed and the percent moisture absorption was calculated using the formula:
% Moisture Absorption = x 100 Wi x Wf Wi

In Vitro Disintegration Test:
The disintegration time of tablets was determined by using Disintegration test apparatus Tablets were placed in disintegration test assembly and disc was placed on tablets in each glass tube of assembly. The assembly was dipped in a vessel containing 900 ml distilled water at 37°C. The time for disappearance of tablet residue above mesh was noted as disintegration time.

Swelling index studies:
The swelling study was performed on petri dishes containing 1% agar gel. Four tablets were weighed and placed in a petri dish. The petri dishes contained 4 tablets, and each was placed in an incubator at 37 ºC + 1 ºC. After 0.5, 1, 1.5, 2, 2.5, 3 hours, excess water on the surface was carefully removed using the filter paper without pressing. The tablets were reweighed and the swelling index was calculated using the formula:
Swelling Index = x 100 Wi x Wf Wi

Dissolution studies:
In vitro dissolution studies of Buprenorphine buccal tablets formulations prepared were carried out in 900mL of 6.8 phosphate buffer using USP type II (paddle method) Dissolution Rate Test Apparatus (DISSO 8000, Lab India). The tablet was placed in a sinker and placed in to the dissolution medium. A speed of 100 rpm and a temperature of 37± 1ºC were used in each test. A 5mL aliquot was withdrawn at different time intervals, and replaced with 5mL of fresh dissolution medium. The filtered samples were suitably diluted if necessary and assayed for Buprenorphine by measuring absorbance at 269nm. The dissolution experiments were carried out in triplicate.

Stability studies:
Stability studies were carried out of the most satisfactory formulation F4, at 30 ± 2°C / 65 ± 5% RH and 40 ± 2°C / 75 ± 5% RH for two months to assess their long term stability as per ICH guidelines. At various time intervals of 30 days and 60 days and 90 days samples were evaluated. There was no major change in the various physicochemical parameters evaluated like hardness, drug content, in vitro dissolution pattern at the various sampling points. There was no statistically significant difference between the initial values and the results obtained during stability studies.[14]

RESULTS AND DISCUSSION:

Drug - excipient compatibility studies (FT-IR):
FT-IR Spectra of Buprenorphine and excipients were recorded. All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between Buprenorphine and polymers.

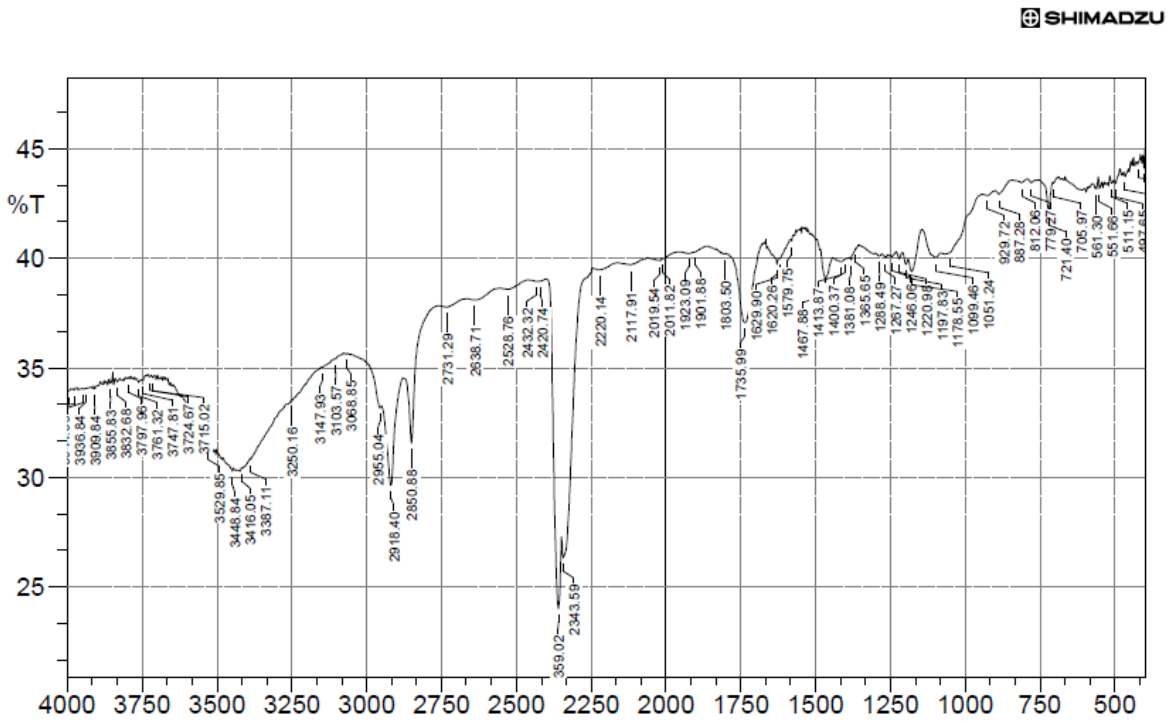

Fig-1: FTIR Spectra of Buprenorphine

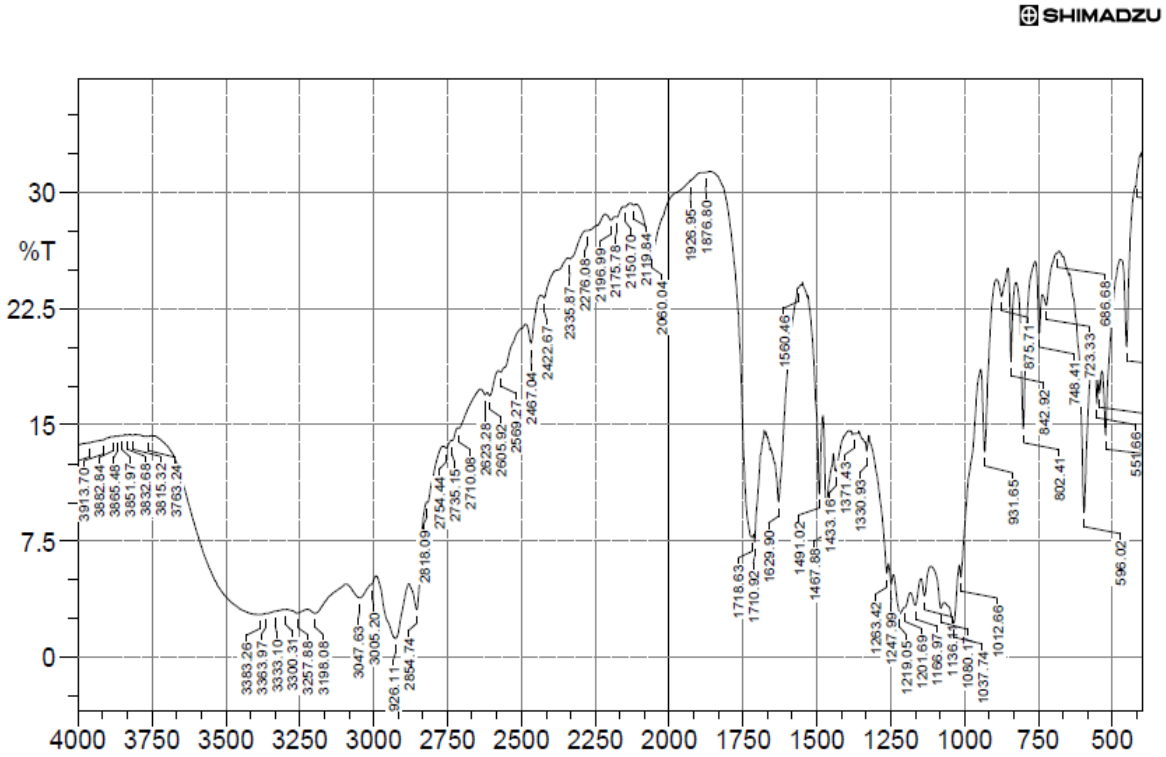

Fig-2: FT-IR graph for optimized formulation

From the figure it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers. This further confirms the integrity of pure drug and compatibility of them with excipients.

Evaluation studies:

Pre-compression parameters

a) **Bulk Density:** The bulk density for the formulated blend was carried out for all formulation and found in the range of 0.448-0.460.

b) **Tapped density:** The tapped density for the formulated blend was carried out for all formulation and found in the range of 0.524-0.536.

c) **Angle of repose:** The angle of repose for the formulated blend was carried out. It concludes that all the formulations blend was found to be in the range of 25 to 30^0

c) **Compressibility index:** Compressibility index was carried out, it found between 16.93% to 17.89 % indicating the powder blend have the required flow property for compression.

Characterization of Formulation:

Table-2: Pre-compression parameters of Buprenorphine tablets

S. no	Bulk density	Tapped density	Compressibility index	Hausner ratio	Angle of repose
F1	0.448	0.528	17.58	1.20	29^0c
F2	0.452	0.530	17.46	1.18	30^0c
F3	0.460	0.524	16.93	1.23	27^0c
F4	0.458	0.536	17.89	1.25	25^0c

Post compression parameters:

Weight variation:

All the formulated (F1 to F4) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness:

Tablets mean thickness were uniform in F1 to F4 formulations and were found to be in the range of 2.5 mm to 3.1 mm.

Hardness:

The measured hardness of tablets of each batch ranged between 3.27 to 3.50 kg/cm^2. This ensures good handling characteristics of all batches.

Friability:

The % Friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity:

The percentage of drug content for F1 to F4 was found to be between 79.83 % to 82.60 % of Buprenorphine, it complies with official specifications.

Disintegration Time:

In the presented studies, three different types of in vitro methods of tablet disintegration were used: those where the only factor leading to the disintegration was water wicking into the matrix of the tablet, the tests with water agitation or stirring, and the methods where direct destructive forces were put on the tested tablet, such as grinding or pressing with additional weight. Therefore, disintegration tests showed great variability in the data measured with different methods.

Table-3: Evaluation parameters of Buprenorphine tablets

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Disintegration time (min)	Swelling index
F1	100	2.9	3.50	0.45	79.83	17	128
F2	99	2.5	3.27	0.43	78.69	15	123
F3	100	2.7	3.29	0.41	81.20	12	127
F4	100	3.1	3.45	0.39	82.60	10	120

Dissolution studies:
All the 4 formulation of Buprenorphine buccal tablets were subjected to in vitro drug release studies these studies were carried out using dissolution apparatus. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for period of time.

Table-4: Drug release studies of all formulations

Time	F1	F2	F3	F4
0	0	0	0	0
1	18.12	17.32	18.10	19.36
2	27.16	28.50	27.46	28.46
3	34.92	35.36	36.90	35.89
4	47.55	48.90	47.86	48.16
5	57.55	58.25	57.14	58.20
6	66.23	67.49	68.90	69.58
7	77.18	78.55	79.82	80.12
8	91.25	92.26	93.67	96.37

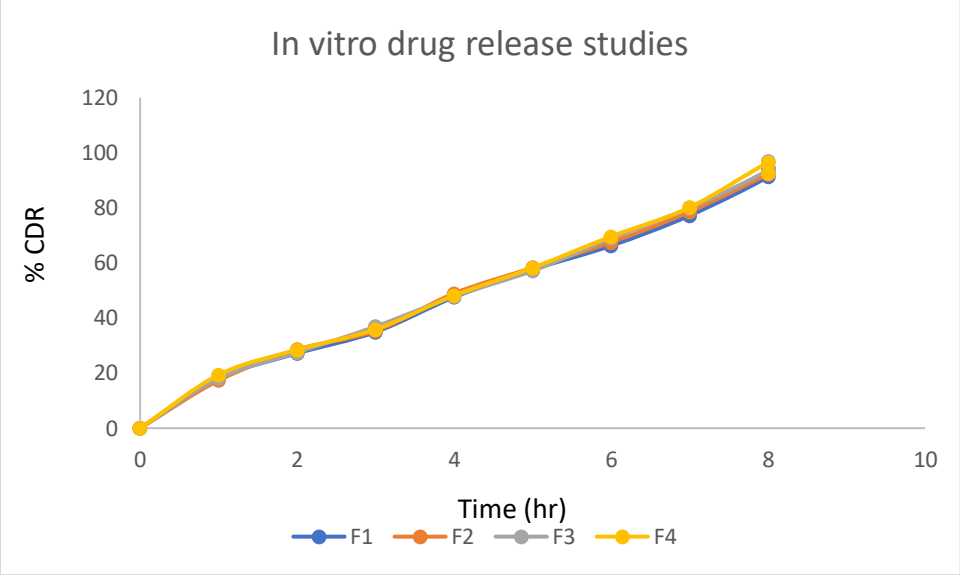

Table-3: Dissolution Profile of F1to F4 formulations

Stability Study:
There was no significant change in physical and chemical properties of the tablets of formulation F-4 after 90 days. Parameters quantified at various time intervals were shown.

Table-5: Stability studies of all formulations

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-4	**25^0C/60%RH % Release**	96.37	95.81	94.82	93.69	**Not less than 85 %**
F-4	**30^0C/75% RH % Release**	96.37	95.76	94.36	93.56	**Not less than 85 %**
F-4	**40^0C/75% RH % Release**	96.37	95.42	94.25	93.40	**Not less than 85 %**

CONCLUSION:

The present study was undertaken with an aim to formulate and evaluate Buprenorphine buccal tablets using different polymers as release retarding agents. Preformulation study was carried out and all the parameters were found within the specification. Hence different batches of Buprenorphine were prepared using selected excipients. Powders were evaluated for Bulk density, tapped density, compressibility index, Hausner ratio before being punched as tablets.

Various formulations of buccal tablets of Buprenorphine were prepared by using different polymers in different proportions by direct compression technique. The buccal tablets were evaluated for physical parameters, *in vitro* release study and stability studies.

In-vitro release indicated that the formulation F4 had better dissolution profile along with sustained action as compare to other formulations. Tablets were evaluated for hardness, friability, in-vitro release profile and drug content. No significant changes were observed in any of the studied parameters during the study period (90days), thus it could be concluded that formulation was stable. From the results it can be concluded that sustained release tablet of Buprenorphine containing HPMC i.e. F4 can be formulated successfully.

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