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Development and evaluation of chlorhexidine mucoadhesive tablets for buccal drug delivery

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ABSTRACT

The present investigation is concern with formulation and evaluation of mucoadhesive buccal tablets containing anti anti-infective agent. Chlorhexidine to circumvent the first pass effect and to improve its bioavailability with reduction in dosing frequency and dose related side effects. The tablets were prepared by direct compression method. Nine formulations were prepared with different polymers like ethyl cellulose, hpmc k 100, eudragit rl with varying concentration. The tablets were tested for weight variation, hardness, drug content uniformity, and *in vitro* drug dissolution study. Ftir studies showed no evidence on interactions between drug and polymer. The *in vitro* release of chlorhexidine was performed under sink conditions (phosphate buffer ph 6.8, $37c^0.5^0c$) using dissolution apparatus usp type ii. The best *in vitro* drug release profile was achieved with the formulation f3 which contains the drug, hpmc k 100 (15 mg). The formulation f3 containing 5 mg of chlorhexidine exhibited 8 hrs sustained drug release i.e. 99.14%. The *in vitro* release kinetics studies reveal that formulation fits with higuchi release model.

Key words: chlorhexidine, ethyl cellulose, hpmc k 100, eudragit rl and buccal tablets.

INTRODUCTION

buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of dosing .problems such as first pass metabolism and drug degradation in the git environment can be circumvented by administering the drug via buccal route. Moreover, the oral cavity is easily accessible for self medication and be promptly terminated in case of toxicity by removing the dosage form from buccal cavity. It is also possible to administer drugs to patients who cannot be dosed orally via this route successful buccal drug delivery using buccal adhesive system requires at least three of the following (a) a bioadhesive to retain the system in the oral cavity and maximize the intimacy of contact with mucosa (b) a vehicle the release the drug at an appropriate rate under the conditions prevailing in the mouth and (c) strategies for overcoming the low permeability of the oral mucosa. Buccal adhesive drug delivery stem promote the residence time and act as controlled release dosage forms.

Mechanism of mucoadhasive:

Several theories have been put forward to explain the mechanism of polymer–mucus interactions that lead to

mucoadhesion. To start with, the sequential events that occur during bioadhesion include an intimate contact between the bioadhesive polymer and the biological tissue due to proper wetting of the bioadhesive surface and swelling of the bioadhesive. Following this is the penetration of the bioadhesive into the tissue crevices, interpenetration between the mucoadhesive polymer chains and those of the mucus. Subsequently low chemical bonds can become operative. Hydration of the polymer plays a very important role in bioadhesion. There is a critical degree of hydration required for optimum bioadhesion. If there is incomplete hydration, the active adhesion sites are not completely liberated and available for interaction. On the other hand, an excessive amount of water weakens the adhesive bond as a result of an overextension of the hydrogen bonds. During hydration; there is a dissociation of hydrogen bonds of the polymer chains. The polymer–water interaction becomes greater than the polymer-polymer interaction, thereby making the polymer chains available for mucus penetration. Following polymer hydration intermingling between chain segments of the mucoadhesive polymer with the mucus occurs. The factors critical for this model of mucoadhesion are the diffusion coefficient of the polymer, contact time and contact pressure. The polymer diffusion coefficient is influenced by the molecular mass between cross-links, and is inversely related to the cross-linking density.

MATERIALS AND METHODS

Chlorhexidine procured from lark laboratories, bhiwadi, india. Provided by sura labs, dilsukhnagar, hyderabad. Ethyl cellulose from zydus cadila, ahmedabad. Hpmc k 100 from acurate pharma. Eudragit from rl sd fine chem.ltd. Mumbai. Mcc from chemdie corporation.magnesium stearate from chemdie corporation.talc from sd fine chem.ltd. Mumbai.saccharin sodium from sd fine chem.ltd. Mumbai.

Methodology

Preformulation studies

Analytical method used in the determination of chlorhexidine

Preparation of 0.2m potassium dihydrogen orthophosphate solution: accurately weighed 27.218 gm of monobasic potassium dihydrogen orthophosphate was dissolved in 1000 ml of distilled water and mixed.

Preparation of 0.2m sodium hydroxide solution: accurately weighed 8 gm of sodium hydroxide pellets were dissolved in 1000 ml of distilled water and mixed

Preparation of ph 6.8 phosphate buffer: accurately measured 250 ml of 0.2m potassium dihydrogen ortho phosphate and 112.5 ml of 0.2m naoh was taken into the 1000 ml volumetric flask. Volume was made up to 1000 ml with distilled water.

Preparation of ph 7.4 phosphate buffer: accurately measured 250 ml of 0.2m potassium dihydrogen ortho phosphate and 195.5 ml of 0.2m naoh was taken into the 1000 ml volumetric flask. Volume was made up to 1000 ml with distilled water.

Preparation of standard graph in phosphate buffer ph 6.8

100 mg of pure drug was dissolved in small amount of methanol (5-10 ml), allowed to shake for few minutes and then the volume was made up to 100ml with phosphate buffer ph 6.8, from this primary stock (1mg/ml), 10 ml solution was transferred to another volumetric flask made up to 100 ml with phosphate buffer ph 6.8. From this secondary stock 0.2, 0.4, 0.6, 0.8, 1, ml was taken separately and made up to 10 ml with phosphate buffer ph 6.8 to produce 2, 4, 6, 8, 10 µg/ml respectively. The absorbance was measured at 280 nm using a uv spectrophotometer. Standard calibration curve values were shown in table 8. The standard calibration curve of chlorhexidine in phosphate buffer ph 6.8 was shown in fig 1.

Preparation of standard graph in phosphate buffer ph 7.4

100 mg of drug was dissolved in small amount of phosphate buffer and make the volume up to 100ml with phosphate buffer ph 7.4, from this primary stock(1mg/ml), 10 ml solution was transferred to another volumetric flask made up to 100 ml with phosphate buffer ph 7.4. From this secondary stock 0.2, 0.4, 0.6, 0.8, 1 ml were taken separately and made up to 10 ml with phosphate buffer ph 7.4, to produce 2, 4, 6, 8, 10 µg/ml respectively. The absorbance was measured at 280 nm using a uv spectrophotometer. Standard calibration curve values were shown in table 9. The standard calibration curve of chlorhexidine in phosphate buffer ph 7.4 was shown in fig 2.

Solubility studies

The solubility of chlorhexidine in phosphate buffer solution ph 6.8 was determined by phase equilibrium method. An excess amount of drug was taken into 20 ml vials containing 10 ml of phosphate buffers (ph 6.8). Vials were closed with rubber caps

and constantly agitated at room temperature for 24 hr using rotary shaker. After 24 hr, the solution was filtered through 0.2µm whattman's filter paper. The amount of drug solubilized was then estimated by measuring the absorbance at 280 nm using a uv spectrophotometer.

The standard curves for chlorhexidine were established in phosphate buffers (ph 6.8) and from the slope of the straight line the solubility of chlorhexidine was calculated. The studies were repeated in triplicate (n = 3), and mean was calculated.

Evaluation of pre-compression blend:

The quality of tablet, once formulated, by rule is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characterization of blends produced. Prior to compression, granules were evaluated for their characteristic parameter such as tapped density, bulk density, carr's index, angle of repose, hausner's ratio. Compressibility index was calculated from the bulk and tapped density using a digital tap density apparatus. The various characteristics of blends tested are as given below:

Angle of repose:

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the granules. The granules were allowed to flow through funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

$$\tan\theta = h/r$$

Where, θ = angle of repose
h = height of the cone
r = radius of the cone base

The relationship between the angle of repose and flowability is as follows:

Table 1: angle of repose values

s.no	angle of repose	flowability
1.	<25	excellent
2.	25-30	good
3.	30-40	passable
4.	>40	poor flow

Bulk density:

Density is defined as weight per unit volume. Bulk density ρb, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping and storage of raw material and blend. It is also important in size blending equipment. 30 gm of powder blend introduced into a dry 100 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume v_0, was read. The bulk density was calculated using the formula:

$$\rho b = m/v_0$$

Where, ρb= apparent bulk density.
m=weight of the sample.
v=apparent volume of powder.

Tapped density:

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides a fixed drop of 14±2 mm at a nominal rate of 300 drops per minute. The cylinder was tapped 500 times initially followed by an additional tap of 750 times until difference between succeeding measurement is less than 2% and then tapped volume, v_f was measured, to the nearest graduated unit. The tapped density was calculated, in gm per ml, using the formula:

$$\rho_{tap} = m/v_f$$

Where, ρ_{tap}= tapped density.
m = weight of the sample.
v_f = tapped volume of the powder.

Carr's index:

The compressibility index (carr's index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measure of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the compressibility index which is calculated using the following formula:

$$\textbf{carr's index} = [(\rho_{tap}-\rho b)]/\rho_{tap}]\times 100$$

where, ρb= bulk density

ρ_{tab}= tapped density

Table 2: carr's index values

s.no	carr's index	flowability
1.	5-12	free flowing
2.	13-16	good
3.	18-21	fair to passable
4.	23-35	poor
5.	33-38	very poor
6.	>40	extremely poor

Hausner's ratio:

It is the ratio of tapped density to the bulk density. Hausner's found that this ratio was related to interparticle friction and, as such, could be used to predict powder flow properties. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of carr's index.

$$\textbf{Hausner's ratio} = \rho_{tap}/\rho b$$

Where, ρ_{tap} = tapped density.

ρb = bulk density.

Table 3: hausner's ratio values

s.no	Hausner's ratio	flowability
1.	0-1.2	free flowing
2.	1.2-1.6	cohesive powder

Formulation development of tablets

Buccal tablets were prepared by a direct compression method, before going to direct compression all the ingredients were screened through sieve no.100. Ethyl cellulose, hpmc k 100, eudragit rl are the mucoadhesive polymers used in this preparation of buccal mucoadhesive drug delivery systems.

Chlorhexidine was mixed manually with different ratios of ethyl cellulose, hpmc k 100, eudragit rl and mcc as diluent for 10 min the blend was mixed with talc and magnesium stearate for 3-5 min.

Preparation of tablets:

Then the powder blend was compressed into tablets by the direct compression method using 8mm flat faced punches. The tablets were compressed using a ten station lab press rotary tablet-punching machine. The weight of the tablets was determined using a digital balance and thickness with digital screw gauge. Composition of the prepared bioadhesive buccal tablet formulations of chlorhexidine were given in table 4.

Table 4: formulation chart

Ingredients (mg)	Formulation codes								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Chlorhexidine	5	5	5	5	5	5	5	5	5
Ethyl cellulose	5	10	15	-	-	-	-	-	-
Hpmc k 100	-	-	-	10	20	33	-	-	-
Eudragit rl	-	-	-	-	-	-	30	40	50
Mcc	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s
Magnesium stearate	4	4	4	4	4	4	4	4	4
Talc	5	5	5	5	5	5	5	5	5
Saccharin sodium	15	15	15	15	15	15	15	15	15
Total weight	100	100	100	100	100	100	100	100	100

Evaluation of buccal tablets:

Physicochemical characterization of tablets:

The prepared chlorhexidine buccal tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation:

The weight variation test is done by taking 20 tablets randomly and weighed accurately. The composite weight divided by 20 provides an average weight of tablet. Not more than two of the individual weight deviates from the average weight by 10 % and none should deviate by more than twice that percentage. The weight variation test would be a satisfactory method of determining the drug content uniformity.

The percent deviation was calculated using the following formula:

% deviation = (individual weight – average weight / average weight) x 100

The average weight of tablets in each formulation was calculated and presented with standard deviation.

Table 5: pharmacopoeial specifications for tablet weight variation

average weight of tablets (mg)	maximum % of difference allowed
80 or less	10
More than 80 but less than 250	7.5
250 or more	5

Tablet thickness:

the thickness and diameter of the tablets from production run is carefully controlled. Thickness can vary with no change in weight due to difference in the density of granulation and the pressure applied to the tablets, as well as the speed of the tablet compression machine. Hence this parameter is essential for consumer acceptance, tablet uniformity and packaging. The thickness and diameter of the tablets was determined using a digital vernier caliper. Ten tablets from each formulation were used and average values were calculated. The average thickness for tablets is calculated and presented with standard deviation.

Tablet hardness:

tablet hardness is defined as the force required to breaking a tablet in a diametric compression test. Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand the mechanical shocks during handling, manufacturing, packaging and shipping. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Six tablets were taken from each formulation and hardness was determined using monsanto hardness tester and the average was calculated. It is expressed in kg/cm^2.

Friability:

Tablet hardness is not an absolute indicator of the strength because some formulations when compressed into very hard tablets lose their crown positions. Therefore another measure of the tablet strength, its friability, is often measured. Tablet strength is measured by using roche friabilator. Test subjects to number of tablets to the combined effect of shock, abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm for 4 minutes, dropping the tablets to a distance of 6 inches in each revolution.

a sample of preweighed tablets was placed in roche friabilator which was then operated for 100 revolutions. The tablets were then dedusted and reweighed. Percent friability (% f) was calculated as

$$\text{friability (\%)} = \frac{\text{initial weight of 10 tablets} - \text{final weight of 10 tablets*}}{\text{initial weight of 10 tablets}} \times 100$$

$$F\ (\%) = [wo\text{-}w/w_o] \times 100$$

Where, w_0 is the initial weight of the tablets before the test and

W is the final weight of the tablets after test.

Assay:

six tablets of each formulation were taken and amount of drug present in each tablet was determined. Powder equivalent to one tablet was taken and added in 100ml of ph 6.8 phosphate buffer followed by stirring for 10 minutes. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured by using uv-visible spectrophotometer at 280 nm using ph 6.8 phosphate buffer.

In vitro release studies:

The drug release rate from buccal tablets was studied using the usp type ii dissolution test apparatus. Tablets were supposed to release the drug from one side only; therefore an impermeable backing membrane was placed on the other side of the tablet. The tablet was further fixed to a 2x2 cm glass slide with a solution of cyanoacrylate adhesive. Then it was placed in the dissolution apparatus. The dissolution medium was 500 ml of ph 6.8 phosphate buffer at 50 rpm at a temperature of 37 ± 0.5 °c. Samples of 5 ml were collected at different time intervals up to 8 hrs and analyzed after appropriate dilution by using uv spectrophotometer at 280nm.

Surface ph:

weighed tablets were placed in boiling tubes and allowed to swell in contact with ph 6.8 phosphate buffers (12ml). Thereafter, surface ph measurements at predetermined intervals of 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 h were recorded with the aid of a digital ph meter. These measurements were conducted by bringing a ph electrode near the surface of the tablets and allowing it to equilibrate for 1 min prior to recording the readings. Experiments were performed in triplicate (n=3).

Moisture absorption:

agar (5% m/v) was dissolved in hot water. It was transferred into petri dishes and allowed to solidify. Six buccal tablets from each formulation were placed in a vacuum oven overnight prior to the study to remove moisture, if any, and laminated on one side with a water impermeable backing membrane. They were then placed on the surface of the agar and incubated at 37°c for one hour. Then the tablets were removed and weighed and the percentage of moisture absorption was calculated by using following formula:

$$\%\ \text{moisture absorption} = \frac{\text{final weight} - \text{initial weight}}{\text{initial weight}} \times 100$$

Kinetic analysis of dissolution data:

To analyze the in vitro release data various kinetic models were used to describe the release kinetics.

1. Zero – order kinetic model – cumulative % drug released versus time.
2. First – order kinetic model – log cumulative percent drug remaining versus time.
3. Higuchi's model – cumulative percent drug released versus square root of time.
4. Korsmeyer equation / peppa's model – log cumulative % drug released versus log time.

$$\mathbf{a_t = a_0 - k_0 t}$$

Where, a_t = drug release at time't'.

a_0 = initial drug concentration

k_0 = zero – order rate constant (hr^{-1}).

Zero order kinetics:

Zero order release would be predicted by the following equation:-

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero – order release kinetics, with a slope equal to k_0.

First order kinetics:

First – order release would be predicted by the following equation:-

$$\log c = \log c_0 - k_t / 2.303$$

Where, c = amount of drug remained at time't'.

c_0 = initial amount of drug.

k = first – order rate constant (hr^{-1}).

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line, indicating that the release follow first order kinetics. The constant 'k' can be obtained by multiplying 2.303 with the slope values.

Higuchi's model:

Drug release from the matrix devices by diffusion has been described by following higuchi's classical diffusion equation.

$$q = [d\varepsilon / \tau (2a - \varepsilon cs) cst]^{1/2}$$

Where, q = amount of drug released at time't'.

d = diffusion coefficient of the drug in the matrix.

a = total amount of drug in unit volume of matrix.

cs = the solubility of the drug in the matrix.

ε = porosity of the matrix.

τ = tortuosity.

t = time (hrs) at which 'q' amount of drug is released.

Above equation may be simplified if one assumes that 'd', 'cs', and 'a', are constant. Then equation becomes:

$$q = kt^{1/2}$$

When the data is plotted according to equation i.e. Cumulative drug release versus square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'k'.

Korsmeyer equation / peppa's model:

To study the mechanism of drug release from the buccal tablets of chlorhexidine , the release data were also fitted to the well – known exponential equation (korsmeyer equation / peppa's law equation), which is often used to describe the drug release behavior from polymeric systems.

$$M_t / m_a = kt^n$$

Where, m_t / m_a = the fraction of drug released at time't'.

k = constant incorporating the structural and geometrical characteristics of the drug / polymer system.

n = diffusion exponent related to the mechanism of the release.

Above equation can be simplified by applying log on both sides,

And we get:

$$\text{Log } m_t / m_a = \log k + n \log t$$

When the data is plotted as log of drug released versus log time, yields a straight line with a slope equal to 'n' and the 'k' can be obtained from y – intercept. For fickian release 'n' = 0.5 while for anomalous (non – fickian) transport 'n' ranges between 0.5 and 1.0.

Table 6: mechanism of drug release as per korsmeyer equation / peppa's model

S.no	N value	Drug release
1.	N <0.5	Fickian release
2.	0.5<n<1	Non-fickian release
3.	N>1	Case ii transport

Drug-excipient compatibility studies

Fourier transform infrared spectroscopic studies

a fourier transform – infra red spectrophotometer was used to study the non-thermal analysis of drug-excipient (binary mixture of drug: excipient 1:1 ratio) compatibility. The spectrum of each sample was recorded over the 450-4000 cm^{-1}. Pure drug of chlorhexidine with physical mixture (excipients) compatibility studies were performed.

RESULTS AND DISCUSSION

Solubility studies:

Table 7: solubility studies

S.no	Medium	Amount present (µg/ml)
1	Phosphate ph 6.8 buffer	94.34
2	Phosphate ph 7.4 buffer	86.59

Saturation solubility of chlorhexidine in various buffers were studied and shown in the table 7. The results revealed that the solubility of the chlorhexidine was increased from ph 6.8 to 7.4. The solubility of the chlorhexidine in phosphate buffer ph 6.8 is 94.34µg/ml and it was selected as the suitable media for the release studies because the ph of the phosphate buffer ph 6.8 is nearer to that of buccal mucosa ph.

Standard graph in phosphate buffer ph 6.8 (λ max 281 nm)

Standard graph of chlorhexidine was plotted as per the procedure in experimental method and its linearity is shown in table 8 and fig 1**.** The standard graph of chlorhexidine showed good linearity with r^2 of 0.999, which indicates that it obeys "beer- lamberts" law.

Table 8: standard graph values of chlorhexidine in ph 6.8 phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
2	0.129
4	0.244
6	0.357
8	0.481
10	0.597

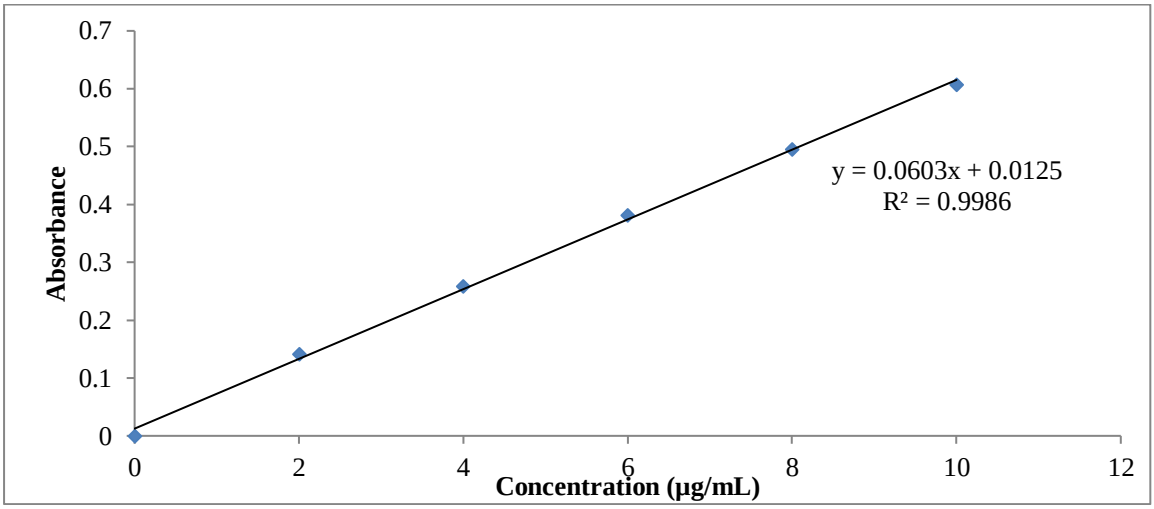

Fig 1: standard graph of chlorhexidine in ph 6.8 phosphate buffer

Standard graph in phosphate buffer ph 7.4 (λ max 282 nm)

Standard graph of chlorhexidine was plotted as per the procedure in experimental method and its linearity is shown in table 9 and fig 2. The standard graph of chlorhexidine showed good linearity with r^2 of 0.998, which indicates that it obeys "beer- lamberts" law.

Table 9: standard graph values of chlorhexidine in ph 7.4 phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
2	0.141
4	0.259
6	0.381
8	0.495
10	0.607

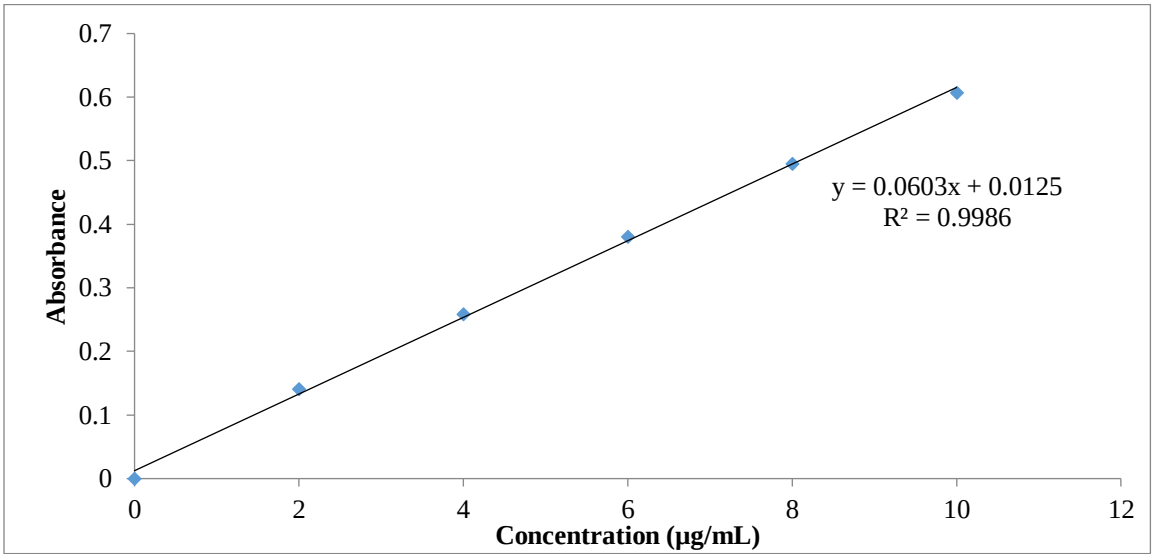

Fig 2: standard graph of chlorhexidine in ph 7.4 phosphate buffer

Evaluation:

Characterization of pre-compression blend: the pre-compression blend of chlorhexidine buccal tablets were characterized with respect to angle of repose, bulk density, tapped density, carr's index and hausner's ratio**.** Angle of repose was less than 29.89º, carr's index values were less than 15.5 for the pre-compression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.18 for all the batches indicating good flow properties.

Table 10: physical properties of pre-compression blend

Formulation code	Angle of repose (ɵ)	Bulk density (gm/cm^3)	Tapped Density (gm/cm^3)	Carr's index (%)	Hausner's ratio
F1	25.35±1.62	0.348±0.047	0.403±0.091	14.28±0.196	1.16±0.011
F2	27.13±1.23	0.347±0.068	0.407±0.066	14.74±0.313	1.17±0.015
F3	29.85±1.44	0.352±0.016	0.407±0.013	13.51±0.282	1.15±0.018
F4	27.13±1.26	0.361±0.033	0.432±0.038	12.96±0.342	1.14±0.016
F5	28.97±1.58	0.355±0.055	0.409±0.073	13.20±0.238	1.15±0.018
F6	29.89±1.45	0.390±0.048	0.462±0.013	15.58±0.237	1.18±0.015

F7	26.90±1.23	0.46±0.017	0.480±0.027	14.58±0.26	1.17±0.012
F8	28.98±1.57	0.412±0.012	0.478±0.069	14.22±0.401	1.16±0.019
F9	27.13±1.26	0.376±0.282	0.432±0.038	12.96±0.342	1.14±0.016

Evaluation of buccal tablets:

Physical evaluation of chlorhexidine buccal tablets: the results of the weight variation, hardness, thickness, friability and drug content of the tablets are given in table 11. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 3.4 to 4.0 kg/cm^2 and the friability values were less than 0.87 % indicating that the buccal tablets were compact and hard. The thickness of the tablets ranged from 4.01 – 4.92 mm. All the formulations satisfied the content of the drug as they contained 95.99-99.93 % of chlorhexidine. Thus all the physical attributes of the prepared tablets were found to be practically within control limits.

Table 11: physical evaluation of chlorhexidine buccal tablets

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Content uniformity (%)
F1	96.19	1.89	3.5	0.68	99.41
F2	99.14	1.65	3.9	0.39	98.34
F3	100.08	1.33	3.4	0.87	99.93
F4	99.34	1.18	3.8	0.46	96.21
F5	97.19	1.72	3.7	0.29	97.14
F6	100.12	1.99	3.9	0.37	99.28
F7	100.07	1.86	4.0	0.46	95.99
F8	99.99	1.79	3.4	0.54	96.72
F9	100.24	1.54	3.8	0.60	98.98

In vitro release studies:

In vitro drug release studies were conducted in phosphate buffer ph 6.8 and the studies revealed that the release of chlorhexidine from different formulations varies with characteristics and composition of matrix forming polymers.

Table 12: *in vitro* dissolution data for formulations f1 – f9

Time (h)	Cumulative percente of drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	33.81	30.16	26.05	24.19	22.24	18.86	15.23	12.14	10.41
1	41.26	36.02	31.61	30.34	26.52	22.51	19.56	16.94	14.75
2	50.34	44.70	41.92	37.96	34.09	30.32	27.49	22.37	20.14
3	65.65	50.94	57.86	45.65	42.90	40.51	38.94	34.19	28.43
4	70.08	66.46	60.73	52.24	50.82	48.06	45.37	40.24	36.18
5	86.11	79.28	74.41	60.19	56.33	53.99	50.59	48.83	45.27
6	93.24	87.15	85.64	82.33	75.61	64.81	62.04	60.14	58.54
7		97.46	94.23	90.10	83.52	77.35	76.95	74.72	71.78
8			99.14	95.63	90.82	86.14	83.14	80.83	78.64

From the above graphs it was evident that ethyl cellulose in the concentration of 15mg of polymer of the total tablet weight (f3) drug with other two formulations f1, f2. Where as in f3 formulation the quantity of polymer was high hence it showed more drug retardation with more drug release that is 99.14 % in 8 hrs.

From the above graphs it was evident that hpmc k 100 in the polymer concentration of 10mg (f4) is showing better result 95.63% drug release when compared with other two formulations f5, f6, as the concentration of polymer increases the retarding of drug release decreased.

From the above graphs it was evident that eudragit rl in the polymer concentration 30mg formulation (f7) is showing better result 83.14% drug release when compared with other two formulations. Where as in f8, f9 formulations the concentration become high and the drug release was less.

Table 13: moisture absorption, surface ph of selected formulations

Formulation code	Moisture absorption	Surface ph
F3	94	5.86
F4	86	6.01
F7	78	6.12

The moisture absorption studies give important information of the relative moisture absorption capacities of polymers and it also give information regarding whether the formulations maintain the integrity or not. Among the selected formulations f3 formulation shown good moisture absorption.

The surface ph of the buccal tablets was determined in order to investigate the possibility of any side effects. As an acidic or alkaline ph may cause irritation to the buccal mucosa, it was determined to keep the surface ph as close to neutral as possible. The surface ph of the selected formulations was found to be 5.86 to 6.12 and the ph was near to the neutral. These results suggested that the polymeric blend identified was suitable for oral application and formulations were not irritant to the buccal mucosa.

Release kinetics:

data of *in vitro* release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of chlorhexidine release from buccal tablets. The data was fitted into various kinetic models such as zero, first order kinetics; higuchi and korsmeyer peppas mechanisms and the results were shown in below table.

Table 14: release kinetics and correlation coefficients (r^2)

Cumulative (%) release q	Time (t)	root (t)	log(%) release	log (t)	log (%) remain	release rate (cumulative % release / t)	1/cum% release	Peppas log q/100	% drug remaining	Q01/3	Qt1/3	Q01/3-qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
26.05	0.5	0.707	1.416	-0.301	1.869	52.100	0.0384	-0.584	73.95	4.642	4.197	0.444
31.61	1	1.000	1.500	0.000	1.835	31.610	0.0316	-0.500	68.39	4.642	4.089	0.552
41.92	2	1.414	1.622	0.301	1.764	20.960	0.0239	-0.378	58.08	4.642	3.873	0.769
57.86	3	1.732	1.762	0.477	1.625	19.287	0.0173	-0.238	42.14	4.642	3.480	1.162
60.73	4	2.000	1.783	0.602	1.594	15.183	0.0165	-0.217	39.27	4.642	3.399	1.243
74.41	5	2.236	1.872	0.699	1.408	14.882	0.0134	-0.128	25.59	4.642	2.947	1.695
85.64	6	2.449	1.933	0.778	1.157	14.273	0.0117	-0.067	14.36	4.642	2.431	2.211
94.23	7	2.646	1.974	0.845	0.761	13.461	0.0106	-0.026	5.77	4.642	1.794	2.848
99.14	8	2.828	1.996	0.903	-0.066	12.393	0.0101	-0.004	0.86	4.642	0.951	3.691

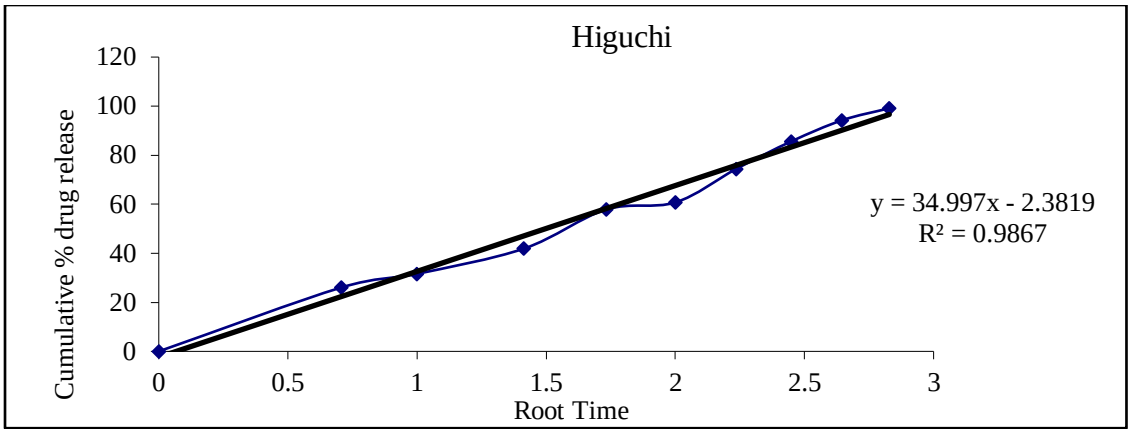

Fig 3: higuchi plot of optimized formulation

this formulation was following higuchi release mechanism with regression value of 0.986.

Drug – excipient compatibility studies by physical observation:

Chlorhexidine was mixed with various proportions of excipients showed no color change at the end of two months, proving no drug-excipient interactions.

Ftir

Ftir spectra of the drug and the optimized formulation were recorded. The ftir spectra of pure chlorhexidine drug, drug with polymers (1:1) shown in the below figures respectively. The major peaks which are present in pure drug chlorhexidine are also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.

There was no disappearance of any characteristics peak in the ftir spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

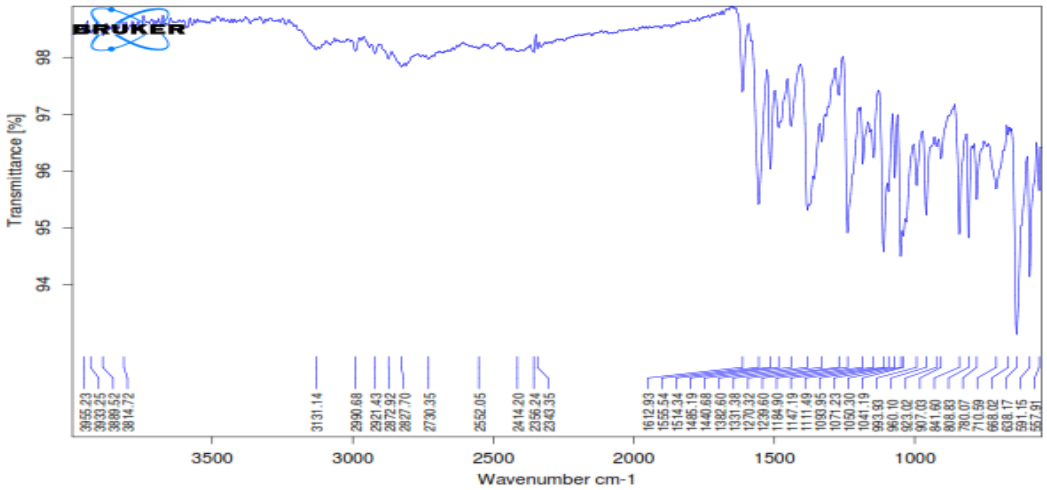

Fig 4: ftir peak of pure drug chlorhexidine

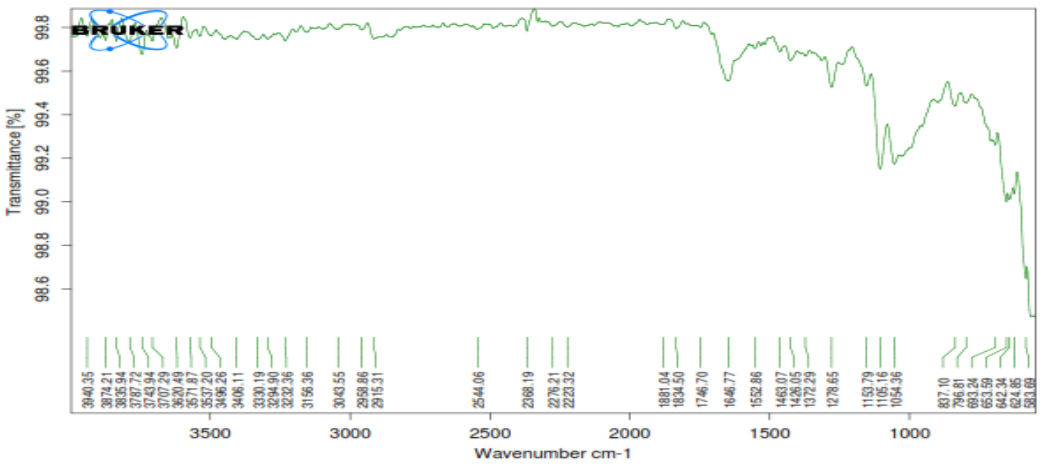

Fig 5: ftir peak of optimised formulation

CONCLUSION

The present study was an attempt to develop bioadhesive drug delivery system for chlorhexidine. The main interest in such a dosage form was made to formulate mucoadhesive buccal tablet for chlorhexidine, in order to avoid extensive first pass metabolism and for prolonged effect. The prepared mucoadhesive buccal tablets subjected to infrared spectrum study suggested that there was no drug - polymer interaction. All the prepared tablets were in acceptable range of weight variation, hardness, thickness, friability and drug content as per pharmacopoeial specification. The surface ph of prepared buccal tablets was in the range of salivary ph, suggested that prepared tablets could be used without risk of mucosal irritation. Mucoadhesive formulations in the form of erodible tablets were developed to a satisfactory level in terms of drug release, physicochemical properties and *in- vitro* drug release could be obtained highest for up to 8 hours with ethyl cellulose polymer. Buccal delivery of chlorhexidine is found to be a promising route for controlling the convulsion. They are found to be more advantageous in comparison to the conventional drug delivery systems containing chlorhexidine. These results guarantee the achievement of therapeutic concentration in the action site, the decrease of drug side effects and the improvement of patient compliance. As such formulation f3 developed is considered as best formulations of chlorhexidine. Thus the study fulfilled the objective of developing efficient buccal tablets of chlorhexidine.

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