CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1214527

Available online at: http://www.iajps.com Research Article

FORMULATION AND EVALUATION OF CEFADROXIL MUCOADHESIVE TABLETS

Y. Krishna Reddy[1]*, S. Ramya Sri[2], Yasarapu Shobha[3]

[1,3]Department of Pharmaceutics, Nalanda College of Pharmacy, Jawaharlal Nehru Technological University, Hyderabad, Telangana

[2]Department of Pharmaceutics, University of Technology, Osmania University, Hyderabad, Telangana

Abstract:

Cefadroxil was formulated as mucoadhesive tablets to improve its bioavailability. Xanthan Gum, Guar Gum , Chitosan and Acritamer 940 were selected as polymers. Various formulations were prepared by using these polymers alone Ex vivo permeation study of Cefadroxil drug solution through the porcine mucosa was performed using franz diffusion cell and the flux value was found to be 400.51 µg.hr-1cm-2, 0.410 cm/hr. The pre-compression blend of Cefadroxil mucoadhesive tablets were characterized with respect to angle of repose, bulk density, tapped density, carr's index and hausner's ratio and all the results indicated that the blend was having good flow nature and better compression properties. The swelling studies were performed for the formulations which were shown desired drug release. Peak detachment force (N) and work of adhesion were calculated and they were found to be good. F5 formulation was showing 94.9% drug release in 8 hrs and following Korsmeyer peppas mechanism with regression value of 0.993. F5 formulation was showing maximum flux value of 382.445 (µg.hrs-1cm-2) and permeability coefficient value was 0.422 (cm/hrs). So based on the results F5 was found to be an optimised formula and concluded that Cefadroxil can used as mucoadhesive tablets.

Keywords: *Mucoadhesive tablets, Cefadroxil, Bioadhesive polymers, Flux, Permeability coefficient.*

Corresponding author:

Y. Krishna Reddy,

Associate Professor,

Department of Pharmaceutics,

Bomma Institute of Pharmacy

Khammam.

QR code

Please cite this article in press Y. Krishna Reddy et al., ***Formulation and Evaluation of Cefadroxil Mucoadhesive Tablets,*** *Indo Am. J. P. Sci, 2018; 05(04).*

INTRODUCTION

The mucosa region of the oral cavity is an attractive target for administration of the drug of choice. mucoadhesive delivery involves the administration of the desired drug through the mucoadhesive mucosal membrane lining of the oral cavity. Unlike oral drug delivery, which presents a hostile environment for drugs, especially proteins and polypeptides, due to acid hydrolysis and the hepatic first-pass effect, the mucosal lining of mucous tissues provides a much milder environment for drug absorption [1-3]. The mucosa is a useful route for the treatment of either local or systemic therapies overcoming the drawbacks of conventional administration routes.

The sites of drug administration in the oral cavity include the floor of the mouth (sublingual), the inside of the cheeks (buccal) and the gums (gingival). mucoadhesive and sublingual sectors are the most appropriate for drug delivery and they may be used for the treatment of local or systemic diseases [1]. The sublingual mucosa is more permeable and thinner than the buccal mucosa and, because of the considerable surface area and high blood flow; it is a feasible site when a rapid onset is desired. The sublingual route is generally used for drug delivery in the treatment of acute disorders, but it is not always useful because its surface is constantly washed by saliva, and tongue activity makes it difficult to keep the dosage form in contact with the mucosa for an extended period of time. Unlike the sublingual mucosa, the buccal mucosa offers many advantages because of its smooth and relatively immobile surface and its suitability for the placement of a retentive sustained or controlled release system, well accepted by patients. The buccal mucosa is relatively permeable, robust and, in comparison with other mucosal tissues, is more tolerant to potential allergens and has a reduced tendency to irreversible irritation or damage. So, it has been largely investigated as a potential site for controlled drug delivery in various chronic systemic therapies [4-8].

Advantages [3]

- The oral mucosa has a rich blood supply. Drugs are absorbed from the oral cavity through the oral mucosa, and transported through the deep lingual or facial vein, internal jugular vein and braciocephalic vein into the systemic circulation. Following administration, the drug gains direct entry into the systemic circulation thereby bypassing the first pass effect.
- It is richly vascularized and more accessible for administration and removal of dosage forms.
- No hepatic first-pass effect
- No pre-systemic metabolism in the gastrointestinal tract
- Ease of administration
- High patient accessibility.

Disadvantages

- Low permeability of mucous membrane specifically when compared to the sublingual membrane.
- Small surface area (170 cm^2).
- Saliva (0.5–2 L/day) is continuously secreted into the oral cavity diluting drugs at the site of absorption resulting in low drug concentrations at the surface of the absorbing membrane.

Anatomy of oral mucosa

The oral mucosa were shown in Figure.1 is made up of a thick, non-keratinized, squamous cell epithelium, overlying a thin lamina propria. Anatomically, the oral mucosa is located between the mucosal lining of the gastrointestinal tract and the skin of the outer face displaying properties of both tissues, Oral mucosa is approximately 500 µm in depth .Mucosal thickness is directly associated with male gender and indirectly associated with age. Non-keratinized mucosa is significantly thicker then keratinized mucosa and successfully withstands the rigorous shearing forces of a prosthesis following oral mucosa transplantation in the oral cavity. Furthermore, non-keratinized mucosa contains more elastic fibers than keratinized mucosa [9-12].

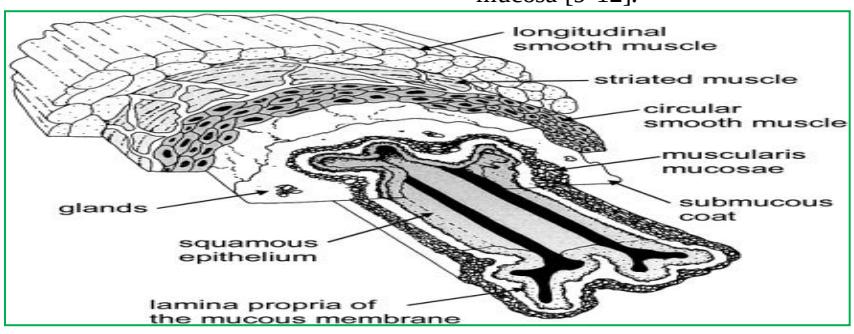

Fig. 1: Structure of oral mucosa

MATERIALS AND METHODS:

Materials Used:

Cefadroxil was a gift sample Provided by Sura Labs, Dilsukhnagar. Xanthan gum, Guar gum, Chitosan, Acritamer 940, Poly vinyl pyrrolidine k 30, Microcrystalline cellulose, Talc, Magnesium stearate, were obtained from Sd fine Chem.Ltd. Mumbai, India.

Methodology

Table 1: The Composition of Mucoadhesive Tablets of Cefadroxil.

Formulation code		F1	F2	F3	F4	F5	F6	F7	F8	F9
Ingredients (mg)	CEFADROXIL	20	20	20	20	20	20	20	20	20
	Xanthan gum	10	20	30	-	-	-	-	-	-
	Guar gum	-	-	-	10	20	30	-	-	-
	Chitosan	-	-	-	-	-	-	10	20	30
	Acritamer 940	10	10	10	10	10	10	10	10	10
	PVP In Iso propyl alcohol 3%	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
	Mg. stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
	Microcrystalline cellulose	105	95	85	105	95	85	105	95	85
	Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total weight in mg		150	150	150	150	150	150	150	150	150

Evaluation Parameters and Procedure

Physicochemical characterization of tablets:

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

A. 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 2: 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

B. 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 tablet is calculated and presented with standard deviation.

C. 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.

D. 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
Friability (%) = Initial weight of 10 tablets – final weight of 10 tablets / Initial weight of 10 tablets X 100

$F(\%) = [Wo-W/W_O] X100$

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

W is the final weight of the tablets after test.

E. 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 100 mL of pH 6.8 phosphate buffer followed by stirring for 10 minutes. The solution was filtered through a 0.45 µ membrane filter, diluted suitably and the absorbance of resultant solution was measured by using UV-Visible spectrophotometer at 238 nm using pH 6.8 phosphate buffer.

***In vitro* release studies:**
The drug release rate from mucoadhesive 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 238nm.

Swelling Studies:
Mucoadhesive tablets were weighed individually (designated as W_1) and placed separately in petridishes containing 15 mL of phosphate buffer (pH 6.8) solution. At regular intervals (0.5, 1, 2, 3, 4, 5 and 6 hrs), the mucoadhesive tablets were removed from the petridishes and excess surface water was removed carefully using the filter paper. The swollen tablets were then reweighed (W_2**)**. This experiment was performed in triplicate. The swelling index (water uptake) calculated according to the following Eq**.**

$$\text{Swelling index} = \frac{(W_2 - W_1)}{W_1} X\ 100$$

***In vitro* bioadhesion strength:**
Bioadhesion strength of tablets were evaluated using a microprocessor based on advanced force gauge equipped with a motorized test stand (Ultra Test Tensile strength tester, Mecmesin, West Sussex, UK) according to method describe as it is fitted with 25 kg load cell, in this test porcine membrane was secured tightly to a circular stainless steel adaptor and the mucoadhesive tablet to be tested was adhered to another cylindrical stainless steel adaptor similar in diameter using a cyanoacrylate bioadhesive. Mucin 100 µL of 1% w/v solution was spread over the surface of the mucosa and the tablet immediately brought in contact with the mucosa. At the end of the contact time, upper support was withdrawn at 0.5 mm/sec until the tablet was completely detached from the mucosa. The work of adhesion was determined from the area under the force distance curve.

The peak detachment force was maximum force to detach the tablet from the mucosa.

$$\text{Force of adhesion} = \frac{\text{Bioadhesion strength x}\ 9.8}{1000}$$

$$\text{Bond strength} = \frac{\text{Force of adhesion}}{\text{surface area}}$$

Surface pH : Weighed tablets were placed in boiling tubes and allowed to swell in contact with pH 6.8 phosphate buffer (12mL). Thereafter, surface pH measurements at predetermined intervals of 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 hrs 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 petridishes and allowed to solidify. Six mucoadhesive 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:

% Moisture Absorption = Final weight – Initial weight / Initial weight x 100

***Ex vivo* residence time:**

The *ex vivo* residence time is one of the important physical parameter of mucoadhesive tablet. The adhesive tablet was pressed over excised pig mucosa for 30 sec after previously being secured on glass slab and was immersed in a basket of the dissolution apparatus containing around 500 mL of phosphate buffer, pH 6.8, at 37^{O}C. The paddle of the dissolution apparatus as adjusted at a distance of 5 cm from the tablet and rotated at 25 rpm Fig . The time for complete erosion or detachment from the mucosa was recorded.

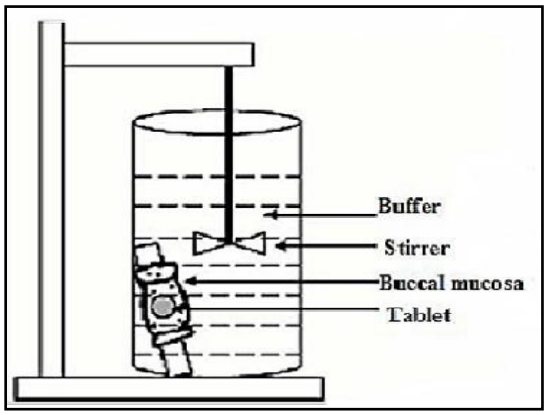

Fig 2: Schematic representation of *Ex vivo* residence time study

***Ex vivo* permeation of mucoadhesive tablets:**

Ex vivo permeation study of Cefadroxil mucoadhesive tablets through the porcine mucoadhesive mucosa was performed using franz-type diffusion cell with a diffusion area of 30.02 cm^2 and the receptor compartment volume of 21 mL at 37°C ± 0.2°C and 50 rpm. This temperature and rpm was maintained by using magnetic stirrer. Porcine mucoadhesive mucosa was obtained from a local slaughterhouse and used within 2hrs of slaughter. The tissue was stored in krebs buffer at 4°C upon collection. The epithelium was separated from underlying connective tissues with surgical scissors and clamped between donor and receiver chambers of the franz-type diffusion cell. After the mucoadhesive membrane was equilibrated for 30 min with krebs buffer solution between both the chambers, the receiver chamber was filled with fresh pH 7.4 buffer solution.

The mucoadhesive tablet was placed in donor chamber and wetted with 1mL of buffer solution (pH 6.8). The amount of drug permeated through the membrane was determined by removing aliquots (5 mL) were collected from the receiver chamber at predetermined time intervals and filtered through a filter paper and the medium of the same volume (5 mL), which was pre-warmed at 37°C, was then replaced into the receiver chamber. The amount of drug permeated through the mucoadhesive mucosa was then determined by measuring the absorbance at 238 nm using a UV spectrophotometer. The experiments were performed in triplicate (n = 3) and mean value was used to calculate the flux (J), permeability coefficient (P).

$$J = \frac{(dQ/dt)}{A}$$

$$P = \frac{(dQ/dt)}{\Delta CA}$$

Where, J is the steady-state flux (mg.hrs^{-1}cm^{-2})

P is permeability coefficient (cm/h)

dQ/dt is the slope obtained from the steady state portion of the curve

ΔC is the concentration difference across the mucosa and

A the area of diffusion (cm^2)

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.

1. Zero order kinetics:

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

$$A_t = A_0 – K_0t$$

Where, A_t = Drug release at time't'.

A_0 = Initial drug concentration

K_0 = Zero – order rate constant (hr^{-1}).

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.

2. 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.

3. Higuchi's model:

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

$$Q = [D\varepsilon / \tau\ (2\ A - \varepsilon Cs)\ Cst]^{1/2}$$

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'.

4. Korsmeyer equation / Peppa's model:

To study the mechanism of drug release from the mucoadhesive tablets of mosapride citrate, 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,:

$$Log\ M_t / M_a = LogK + n\ Logt$$

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 and1

RESULTS AND DISCUSSION:

Drug –Polymer Compatibility Studies by FTIR

Drug polymer compatibility studies were performed by FTIR (Fourier transform infrared spectroscopy). Infrared (IR) spectra were obtained on a (BRUKER IR SYSTEM using the KBr disk method (2 mg sample in 200 mg KBr). The scanning range was 400 to 4000 cm-1 and the resolution was 1 cm^{-1}. FTIR absorption spectra of pure drug and all the polymers used like Xanthan gum, Guar gum, Chitosan, Acritamer 940 and the combination of drug and polymers were shows no significant interaction between drug and polymers. The spectra obtained were shown in the Figure.

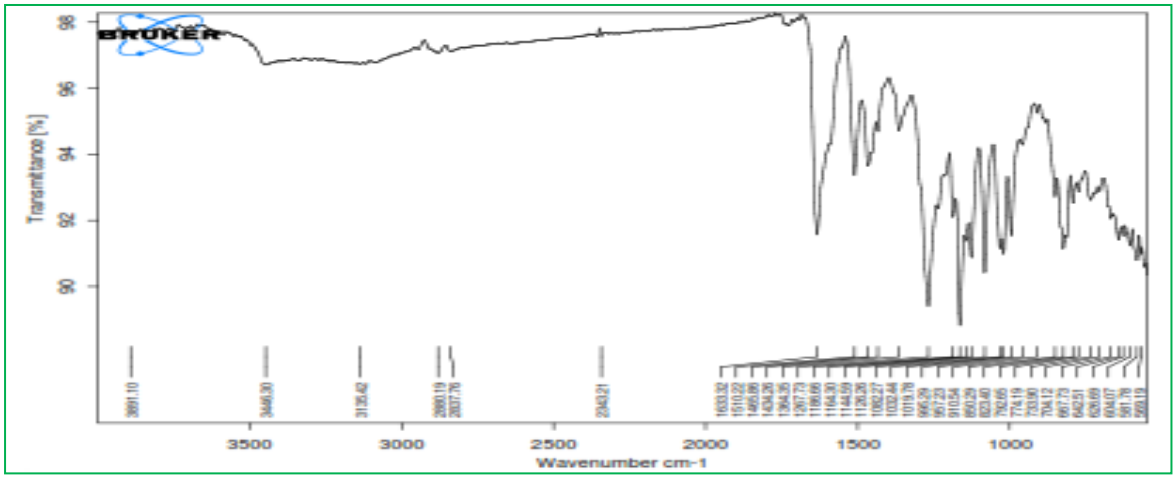

Fig. 3: FTIR of cefadroxil pure drug.

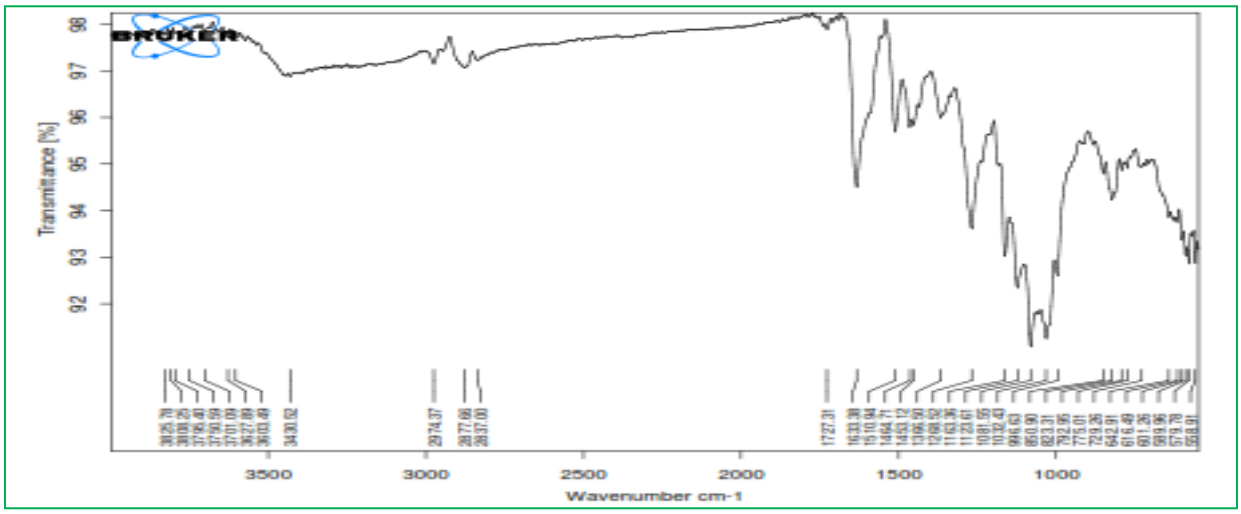

Fig. 4: FTIR Spectra of Optimised Formulation

From the FTIR data it was evident that the drug and excipients doses not have any interactions**.** Hence they were compatible.

Table 3: Calibration curve data for Cefadroxil at 262 nm

CONCENTRATION in µg/ml	ABSORBANCE at 262 nm
0	0
10	0.156
20	0.290
30	0.454
40	0.611
50	0.740

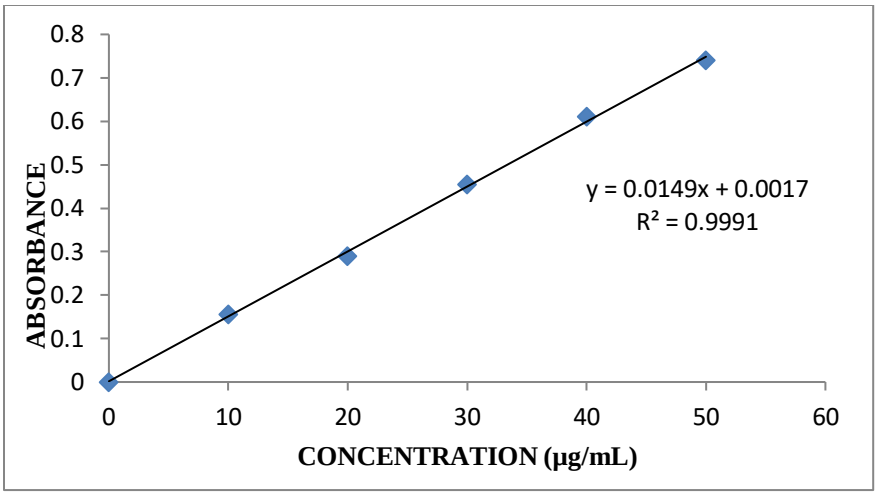

Fig. 5: Standard graph in phosphate buffer pH 6.8

Standard graph in phosphate buffer pH 7.4 (λ_{max} 262 nm)

Standard graph of Cefadroxil was plotted as per the procedure in experimental method and its linearity. The standard graph of Cefadroxil showed good linearity, which indicates that it obeys "Beer- Lamberts" law.

Table 4: Standard graph values of Cefadroxil in pH 7.4 phosphate buffer

S.No	Concentration (µg/mL)	Absorbance
0	0	0
1	10	0.146
2	20	0.292
3	30	0.451
4	40	0.609
5	50	0.738

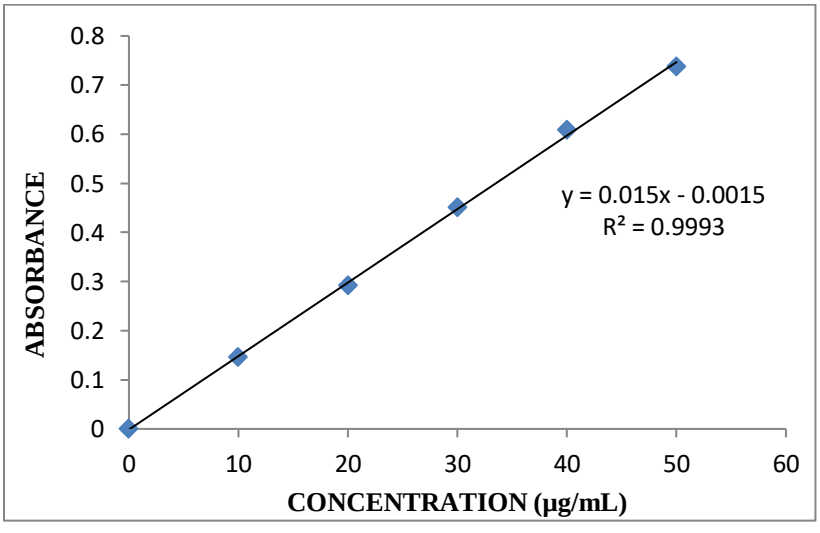

Fig. 6: Standard graph of Cefadroxil in pH 7.4 phosphate buffer

Solubility Studies:

Table 5: Solubility studies

S.No	Medium	Amount present (µg/mL)
1	Phosphate pH6.8 buffer	86
2	Phosphate pH 7.4 buffer	94

Saturation solubility of Cefadroxil in various buffers were studied and shown in the Table. The results revealed that the solubility of the Cefadroxil was increased from pH 6.8 to 7.4. The solubility of the Cefadroxil in phosphate buffer pH 6.8 is 86 µg/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. The results show that this drug exhibits pH dependent solubility.

***Ex vivo* permeation of drug solution through the porcine buccal mucosa**

Ex vivo permeation study of Cefadroxil drug solution through the porcine buccal mucosa was performed using Franz diffusion cell. The membrane assembly was kept at 37±0.2° C and 500 rpm. Temperature and rpm was maintained by the mortarically controlled magnetic stirrer. Phenol red was used as marker compound and is not expected to permeate through porcine membrane. Absence of phenol red in the receiver compartment indicates the intactness of the buccal membrane.

Table 6: Standard values of Phenol red

S.No	Concentration (µg/mL)	Absorbance
1	0	0
2	1	0.09
3	5	0.143
4	7	0.198
5	10	0.264
6	20	0.542
7	25	0.654
8	30	0.792
9	35	0.881

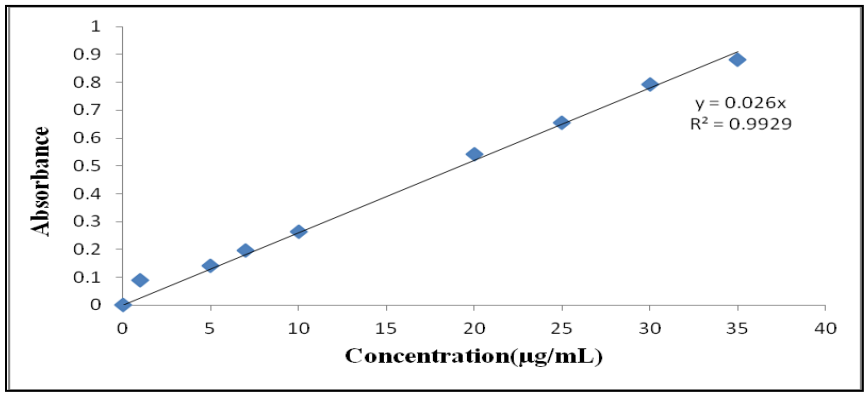

Fig. 7: Standard graph of Phenol red

Table 7: *Ex vivo* permeation of Cefadroxil drug through the porcine mucosa

Time (hrs)	Cumulative amount of cefadroxil permeated (%)
0	0
0.5	10.87
1	14.34
2	17.86
3	26.38
4	33.91
5	42.45
6	70.78
7	90.39
8	93.53
Flux	**400.51 µg.hr^{-1}cm^{-2}**

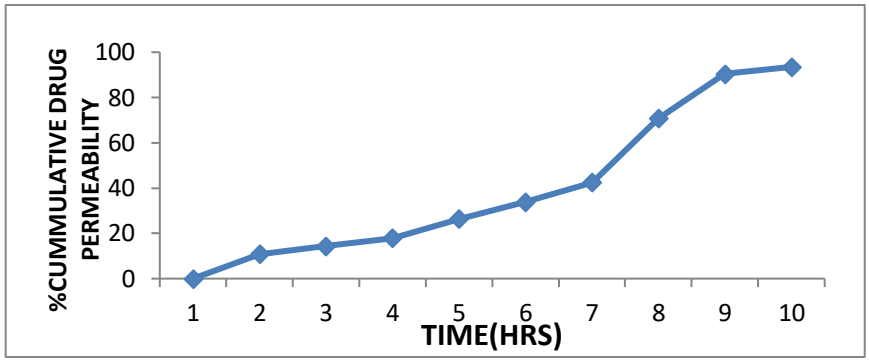

Fig. 8: Graph *Ex vivo* permeation of Cefadroxil drug through the porcine mucosa

The tissue could be isolated successfully because no detectable level of phenol red (Marker compound) was observed in the receiver compartment. Hence it did not show any penetration and shows the intactness of the porcine buccal mucosa. The flux, permeability coefficient were found to be 400.51 µg.hr-1cm-2, 0.410 cm/hr respectively**.**

Evaluation:

Characterization of pre-compression blend: The pre-compression blend of Cefadroxil mucoadhesive tablets were characterized with respect to angle of repose, bulk density, tapped density, carr's index and hausner's ratio**.** Angle of repose, carr's index values for the pre-compression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio for all the batches indicating good flow properties

Table 8: Results for Derived and Flow properties

Formulation Code	Derived properties		Flow properties		
	Bulk density (mean±SD)	Tapped density (mean±SD)	Angle of repose (mean±SD)	Carr's index (mean±S)	Hausner's ratio (mean±SD)
F1	0.437±0.01	0.493±0.015	26.45±0.30	11.44±1.97	1.129±0.02
F2	0.447±0.015	0.503±0.02	27.21±0.39	11.22±1.96	1.126±0.03
F3	0.493±0.015	0.56±0.01	24.97±0.68	11.86±3.97	1.135±0.05
F4	0.476±0.015	0.526±0.015	23.21±0.96	9.48±1.81	1.105±0.02
F5	0.433±0.02	0.496±0.03	25.94±0.73	12.65±2.25	1.145±0.03
F6	0.42±0.01	0.463±0.006	24.25±0.36	9.32±3.16	1.103±0.04
F7	0.453±0.025	0.536±0.025	28.21±0.29	15.54±1.19	1.184±0.02
F8	0.45±0.01	0.51±0.017	23.87±0.40	11.69±3.61	1.126±0.05
F9	0.41±0.01	0.457±0.025	25.17±0.34	10.87±2.84	1.113±0.04

All the values represent mean ± Standard deviation (SD), n=3

Table 9: Evaluation of Mucoadhesive Tablets Of Cefadroxil

Formulation Code	Thickness (mm) ± SD	Average Weight (mg ± SD)	Hardness (Kg/cm^2)	Friability (%)	Content uniformity	Surface pH ± SD
F1	3.52 ±0.06	147±0.97	4.5±0.34	0.420	99±0.12	6.41±0.061
F2	3.59±0.01	149±0.95	4.6±0.25	0.341	99±0.30	6.73±0.03
F3	3.51±0.06	148±0.85	4.8±0.36	0.363	100±0.10	6.62±0.026
F4	3. 56±0.07	150±0.76	4.5±0.26	0.561	100±0.30	6.79±0.040
F5	3.96±0.07	148±0.65	4.6±0.18	0.531	99±0.10	6.67±0.045
F6	3.76±0.05	147±0.92	4.4±0.76	0.513	99±0.40	6.77±0.066
F7	3.68±0.06	149±0.52	4.3±0.86	0.412	98±0.90	6.77±0.061
F8	3.59±0.01	150±0.62	4.8±0.26	0.432	99±0.10	6.56±0.066
F9	3.98±0.07	150±0.82	4.7±0.11	0.512	100±0.10	6.76±0.045

All the values represent mean ± Standard deviation (SD), n=3

***In vitro* release studies [13-15]:**

In vitro drug release studies were conducted in phosphate buffer pH 6.8 and the studies revealed that the release of Cefadroxil from different formulations varies with characteristics and composition of matrix forming polymers as shown in graphs.

Table 10: *In vitro* dissolution data for formulations F1 - F3 by using Xanthan gum Polymer.

Time(hrs)	% Cumulative drug release		
	F1	F2	F3
0	0	0	0
0.5	25.73	17.73	11.42
1	30.04	21.42	13.27
2	45.92	24.90	21.42
3	59.06	33.56	28.95
4	77.57	44.93	34.21
5	82.08	56.40	38.54
6	93.90	64.58	47.54
7	99.56	78.92	48.94
8	-	88.73	58.64

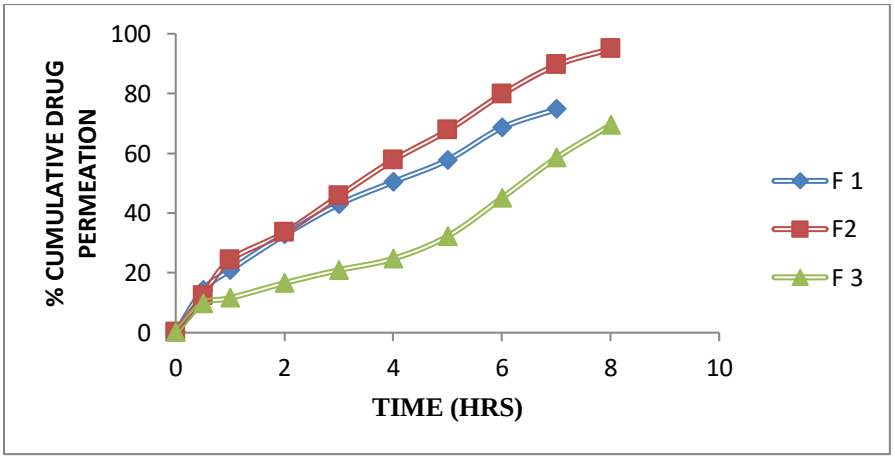

Fig. 9: *In vitro* dissolution data for formulations F1 - F3 by using Xanthan gum polymer

From the above graphs it was evident that Xanthan gum in the concentration of 1:2 (F2) drug with other two ratios 1:1, 1:3 drug polymer ratios. In case of F1 formulation the polymer quantity was in sufficient to produce the required retarding nature upto 8 hrs, maximum drug release was occured in 6 hrs only, where as in F3 formulation the quantity of polymer was because high hence it showed more drug retardation with less drug release that is 58.64 % in 8 hrs.

Table 11: *In vitro* dissolution data for formulations F4 - F6 by using Guar gum polymer

Time(hrs)	% Cumulative drug release		
	F4	F5	F6
0	0	0	0
0.5	14.23	12.36	9.73
1	20.91	24.21	11.56
2	32.73	33.45	16.59
3	42.93	45.69	20.94
4	50.42	57.69	24.72
5	57.75	67.63	32.23
6	68.56	79.68	45.06
7	74.73	89.47	58.43
8	81.90	94.9	69.40

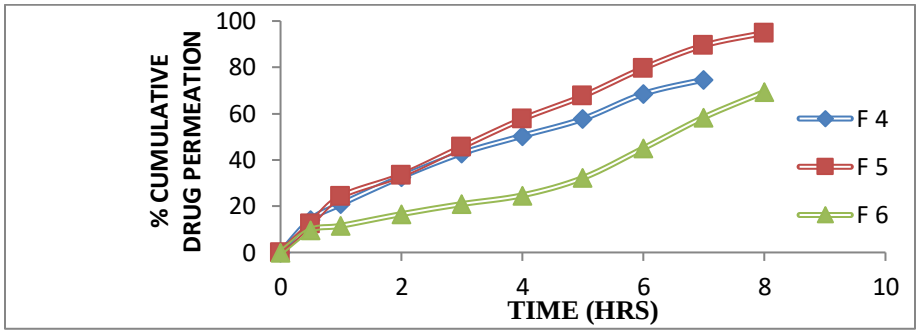

Fig. 10: *In vitro* dissolution data for formulations F4 - F6 by using Guar gum polymer

From the above graphs it was evident that Guar gum in the concentration of 1:2 (F5), drug to polymer ratio, is showing better result 94.90% drug release when compared with other two ratios 1:1, 1:3 drug polymer ratios.

Table 12: *In vitro* dissolution data for formulations F7 - F9 by using Chitosan polymer

Time(hrs)	% Cumulative drug release		
	F7	F8	F9
0	0	0	0
0.5	23.40	16.66	11.06
1	35.56	26.83	16.72
2	49.91	36.59	21.07
3	63.06	44.25	34.45
4	70.73	53.55	41.09
5	82.72	67.58	47.56
6	95.91	78.73	53.43
7	98.23	89.62	60.73
8	-	92.06	70.48

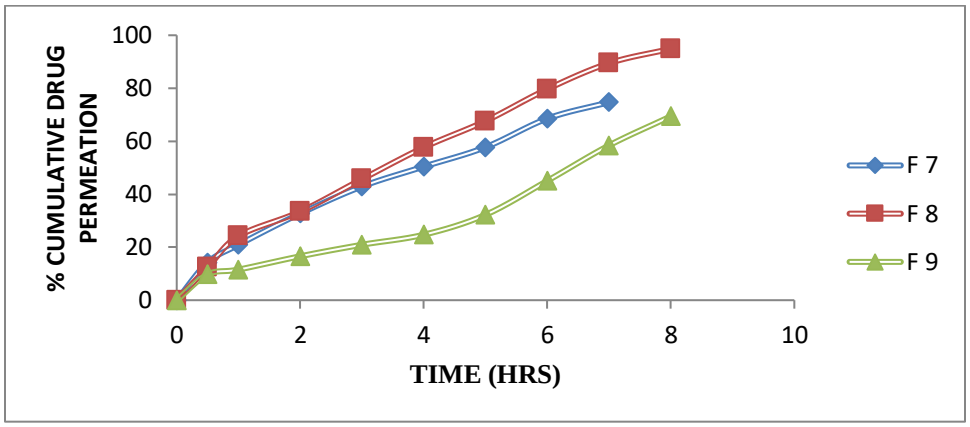

Fig. 11: *In vitro* dissolution data for formulations F7- F9 by using Chitosan polymer

From the above graphs it was evident that Chitosan in the concentration of 1:2 (F8), drug to polymer ratio, is showing better result 92.06% drug release when compared with other two ratios 1:1, 1:3 drug polymer ratios. In case of F7 formulation the polymer was insufficient to produce required bioadhesion strength and the maximum drug was released in 6 hrs only where as in F9 formulation the concentration become high and the drug release was retarded more than 8 hrs, hence it was not taken in to consideration.

***Ex vivo* residence time, moisture absorption, surface pH, bioadhesion strength values of selected formulations [16-20]**

Table 13: *Ex vivo* residence time, moisture absorption, surface pH, bioadhesion strength values of selected formulations.

Formulation Code	*Ex vivo* residence time (hrs)	Moisture absorption	Surface pH	Bioadhesion strength	
				Peak detachment force (N)	Work of adhesion (mJ)
F2	6hr 33min	44±0.25	6.81±0.25	3.8±0.41	17.42±6.10
F5	8hr 5min	66±0.33	6.84±0.04	4.8±0.12	23.41±6.18
F8	7hr 34min	46±0.25	6.74±0.25	3.6±0.22	12.42±6.16

Each value represents the mean±SD (n=3)

***Ex vivo* residence time** is one of the important physical parameter of buccal bioadhesive tablets. The *ex vivo* residence time was determined by specially designed apparatus. Among the selected formulations F5 formulation has shown more residence time when compared with other formulations.

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 F5 formulation shown good moisture absorption.

The surface pH of the mucoadhesive tablets was determined in order to investigate the possibility of any side effects. As an acidic or alkaline pH may cause irritation to the 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 6.71±0.10 to 6.84±0.04 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.

Bioadhesion strength was measured for the selected formulations**.** From this two parameters such as peak detachment force (N) and work of adhesion were calculated and they were found to be good for the formulation F5. The peak detachment force and work of adhesion values were found to be less when the polymers were used individually in case of F2, F4, F8 formulations but when the polymers were taken in combination they showed desired values, in turn F11 that is composed of guar gum showed high value than the of others.

Swelling studies

Table 14: Swelling index of selected formulations

Time (hrs)	Swelling index		
	F2	F5	F8
0	0	0	0
0.5	11.1	12.4	11.3
1	18.3	21.5	17.4
2	24.3	26.3	20.1
3	25.3	30.1	23.1
4	31.1	34.3	30.3
5	42.2	42.2	38.1
6	51.3	56.3	44.3
7	63.4	68.4	53.3
8	68.5	82.3	58.2

Each value represents the mean (n=3)

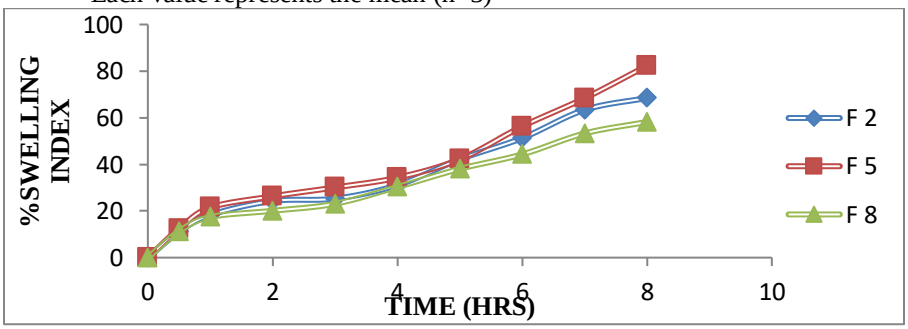

Fig. 12 : Swelling studies of Cefadroxil selected mucoadhesive tablets

The swelling studies were performed for the formulations which were shown desired drug release. Swelling behavior of a mucoadhesive system was essential for uniform and prolonged release of drug and proper bioadhesion. The of polymers containing guar gum was shown good swelling index when compared the formulations.

***Ex vivo* permeation studies through porcine buccal mucosa**

The aim of this study was to investigate the permeability of mucosa to Cefadroxil. It is based on the generally accepted hypothesis that the epithelium is the rate-limiting barrier in the mucous absorption was shown in table & fig.

Table 15: *Ex vivo* permeation studies of optimised formulations through porcine mucosa

Time (hrs)	F5
0	0
0.5	10.68
1	13.34
2	17.24
3	26.82
4	33.38
5	40.6
6	67.8
7	91.39
8	93.23
Flux ($\mu g.hrs^{-1}cm^{-2}$)	382.445
Permeability coefficient (cm/hr)	0.422

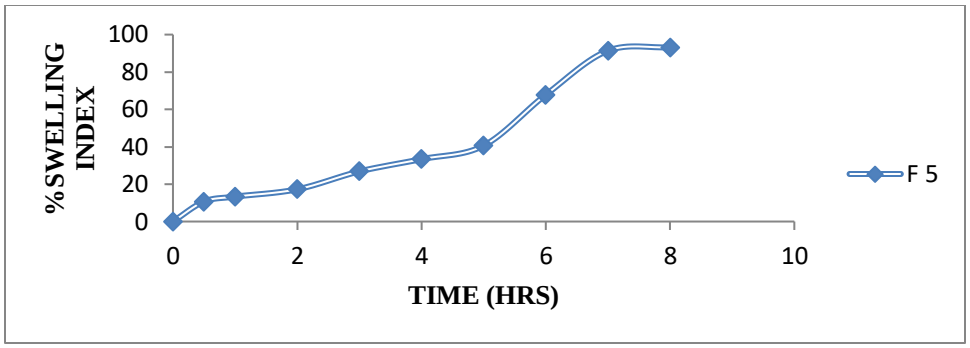

Fig. 13: *Ex vivo* permeation studies graph of selected formulations through porcine buccal mucosa

From the Table it was evident that selected formulations were showing good flux and permeability coefficient values. Among the selected formulations F5 formulation was showing maximum flux value of 382.445 (µg.hrs^{-1}cm^{-2}) and permeability coefficient value was 0.422 (cm/hrs).

6. 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 Cefadroxil release from mucoadhesive 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 no 16: Table of release kinetics and correlation factors

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
12.36	0.5	0.707	1.092	-0.301	1.943	24.720	0.0809	-0.908	87.64	4.642	4.442	0.200
24.21	1	1.000	1.384	0.000	1.880	24.210	0.0413	-0.616	75.79	4.642	4.232	0.410
33.45	2	1.414	1.524	0.301	1.823	16.725	0.0299	-0.476	66.55	4.642	4.052	0.589
45.69	3	1.732	1.660	0.477	1.735	15.230	0.0219	-0.340	54.31	4.642	3.787	0.855
57.69	4	2.000	1.761	0.602	1.626	14.423	0.0173	-0.239	42.31	4.642	3.485	1.157
67.63	5	2.236	1.830	0.699	1.510	13.526	0.0148	-0.170	32.37	4.642	3.187	1.455
79.68	6	2.449	1.901	0.778	1.308	13.280	0.0126	-0.099	20.32	4.642	2.729	1.913
89.47	7	2.646	1.952	0.845	1.022	12.781	0.0112	-0.048	10.53	4.642	2.192	2.450
94.9	8	2.828	1.977	0.903	0.708	11.863	0.0105	-0.023	5.1	4.642	1.721	2.920

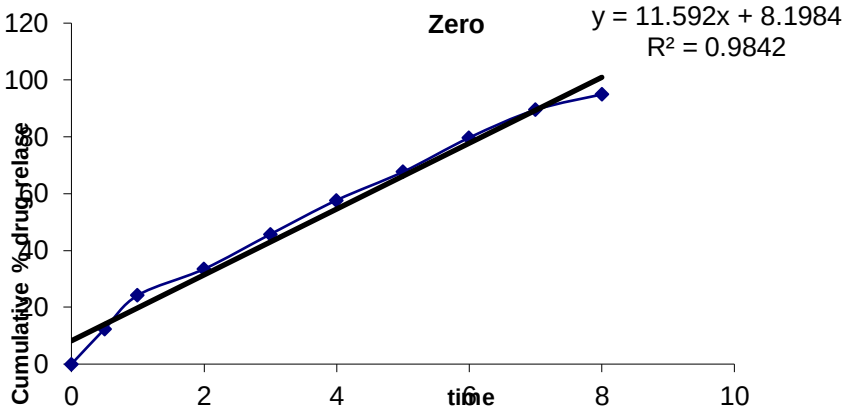

Fig. 14 : Zero order plot of optimized formulation

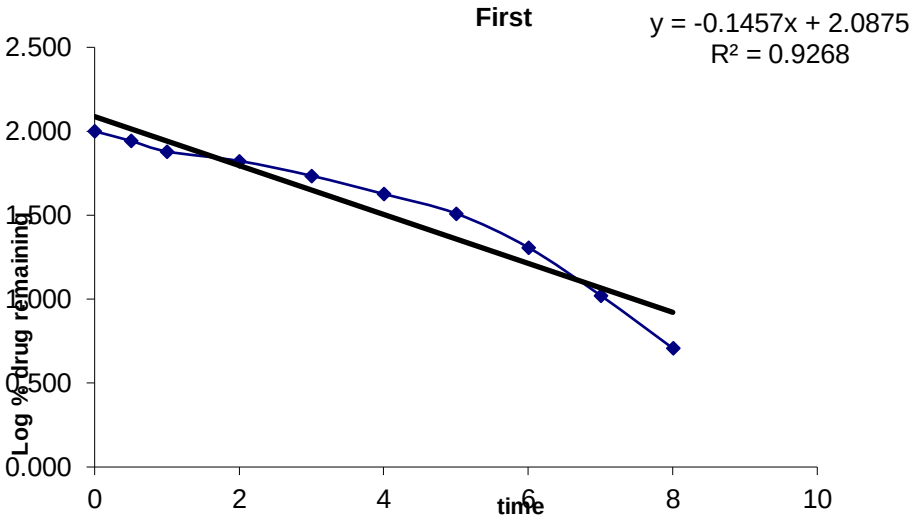

Fig. 15: First order plot of optimized formulation

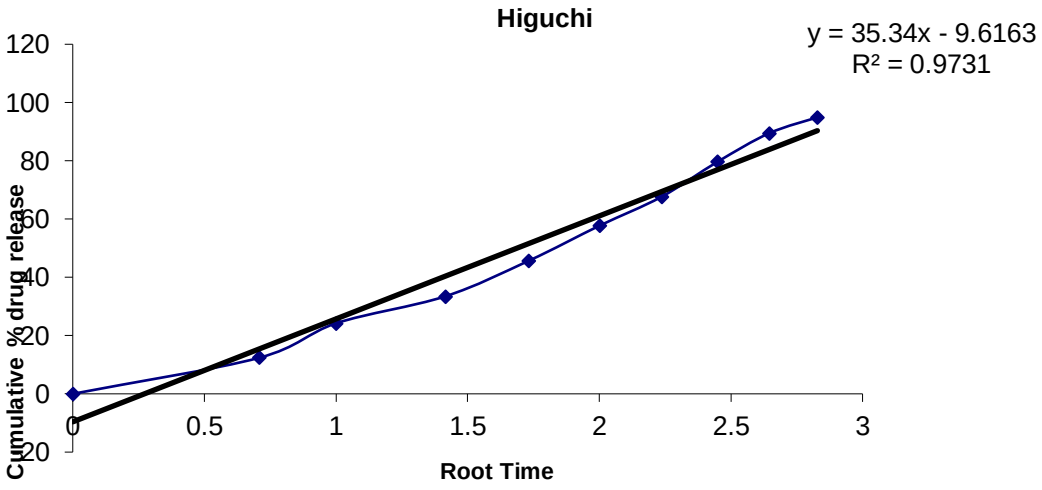

Fig. 16: Higuchi plot of optimized formulation

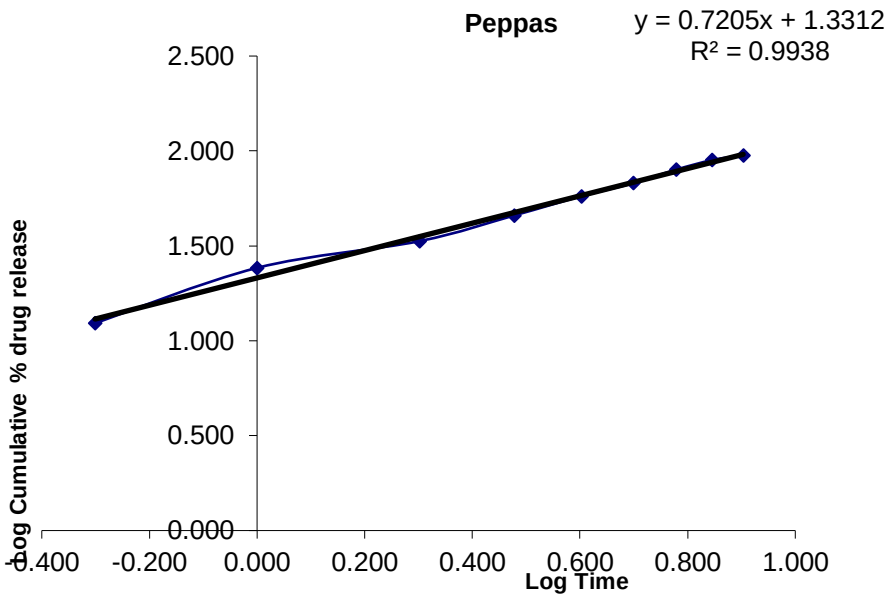

Fig. 17: Koresmeyer-peppas plot of optimized formulation.

Based on the all studies F5 formulation was found to be better when compared with all other formulations. This formulation was following Korsmeyer peppas mechanism with regression value of 0.993.

CONCLUSION:

Cefadroxil was formulated as mucoadhesive tablets to improve its bioavailability. Xanthan Gum, Guar Gum , Chitosan and Acritamer 940 were selected as polymers. Various formulations were prepared by using these polymers alone *Ex vivo* permeation study of Cefadroxil drug solution through the porcine mucosa was performed using franz diffusion cell and the flux value was found to be 400.51 µg.hr-1cm-2, 0.410 cm/hr. The pre-compression blend of Cefadroxil mucoadhesive tablets were characterized with respect to angle of repose, bulk density, tapped density, carr's index and hausner's ratio and all the results indicated that the blend was having good flow nature and better compression properties. The swelling studies were performed for the formulations which were shown desired drug release. Peak detachment force (N) and work of adhesion were calculated and they were found to be good. F5 formulation was showing 94.9% drug release in 8 hrs and following Korsmeyer peppas mechanism with regression value of 0.993. F5 formulation was showing maximum flux value of 382.445 (µg.hrs^{-1}cm^{-2}) and permeability coefficient value was 0.422 (cm/hrs). So based on the results F5 was found to be an optimised formula and concluded that Cefadroxil can used as mucoadhesive tablets.

ACKNOWLWDGEMENT:

The authors are thankful to SURA LABS Dilshukhnagar, Hyderabad, T.S., India for providing the necessary facilities for the research work.

REFERENCES:

1. Nazila salamat-miller, montakarn chittchang, thomas p. Johnston. The use of mucoadhesive polymers in buccal drug delivery. Advanced drug delivery reviews. 2005; 57: 1666– 1691.
2. Oliver a. Scholz, andy wolff, axel schumacher, libero. Giannola, giuseppina campisi, tomasz ciach, thomas velten. Drug delivery from the oral cavity: focus on a novel mechatronic delivery device. Drug discovery today. March 2008; 13: 247-253.
3. M alagusundaram, c madhusudhana chetty, k umasankari, p anitha, k gnanprakash and d dhachinamoorthi. Buccal drug delivery system – an overview. Research j. Pharm. And tech. Oct.-dec. 2009; 2 (4): 653-663.
4. Gerard j. Toratora, bryan derrickson. Principles of anatomy & physiology. 11th edition, willy-international edition; 2007: 902-905.
5. m.j. Rathbone, j. Hadgraft. Absorption of drugs from human oral cavity. Int. J. Pharm 1991; 74: 9–24.

6. Michael r, markiewicz a, joseph e, margarone b. Oral mucosa harvest: an overview of anatomic and biologic considerations. Europeanurology e a u - e b u update e series. 2007; 5:179–187.
7. C.a. Squier, m.w. Finkelstein, a.r. Tencate (ed.). Oral histology, development, structure and function. C.v. Mosby, st. Louis; 1989: 345–385.
8. Janet a.j. Hoogstraate and philip w. Wertz. Drug delivery via the buccal mucosa. Pstt october 1998; 1(7): 309-316.
9. Squier, c.a. The permeability of oral mucosa. Crit. Rev. Oral biol. Med, 1991; 2: 13-32.
10. H.s. Chng, h. Park, p. Kelly, j.r. Robinson. Bioadhesive polymers as platforms for oral controlled drug delivery: ii. Synthesis and evaluation of some swelling, water-insoluble bioadhesive polymers. J. Pharm. Sci 1985; 74: 399– 405.
11. Yajaman sudhakar, ketousetuo kuotsu, a.k.bandyopadhyay. Buccal bioadhesive drug delivery -a promising option for orally less efficient drugs. Journal of controlled release. 2006; 114: 15–40.
12. A. Ahuja, r.k. Khar, j. Ali. Mucoadhesive drug delivery systems. Drug dev. Ind. Pharm. 1997; 23 (5): 489–517.
13. ravi bhalodia, biswajit basu, kevin garala, bhavik joshi and kuldeep mehta. Buccoadhesive drug delivery systems: a review". Ijpbs: 1-25.
14. Saroj kumar roy and bala prabhakar. Bioadhesive polymeric platforms for transmucosal drug delivery systems – a review". Tropical journal of pharmaceutical research, february 2010; 9 (1): 91-104.
15. e. Mathiwitz, d.e. Chickering, c.m. Lehr. Bioadhesive drug delivery systems: fundamentals, novel approaches and development, marcel dekker, inc., new york. 1999: 1-8.
16. Punitha s, girish y. Polymers in mucoadhesive buccal drug delivery system. Int. J. Res. Pharm. Sci. 2010; 1(2): 170-186.
17. Manabu kitano, yoshie maitani, kozo takayama, tsuneji nagai. Buccal absorption through golden hamster cheek pouch in vitro and in vivo of 17β-estradiol from hydrogels containing three types of absorption enhancers. Int. J. Pharm. 1998; 174: 19-28.
18. Aungst, b.j., rogers, n.j. Site dependence of absorption promoting action of laureth– 9, na salicylate, na2 edta and aprotinin on rectal, nasal and buccal insulin delivery. Pharm. Res. 1988; 5: 305- 308.
19. r.b.gandhi, j.r. Robinson. Bioadhesion in drug delivery. Ind. J. Pharm. Sci. 1988; 50 (3): 145–152.
20. Oh c.k, ritschel w.a. Biopharmaceutical aspect of buccal absorption of insulin. Exp. Clin. Pharmacol. 1990; 12: 205-212.