WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 12, 791-807. Research Article ISSN 2277– 7105

FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL TABLETS OF NITRENDIPINE

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Article Received on
26 Sep 2015,

Revised on 16 Oct 2015,
Accepted on 08 Nov 2015

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ABSTRACT

The drug delivery via buccal route is considered to be one of the promising alternative to oral route and quick entry of drug into the systemic circulation through the internal jugular vein. The aim of the present investigation was to develop mucoadhesive buccal tablets of Nitrendipine, a calcium channel blocker through buccal route. Mucoadhesive buccal tablets were formulated by direct compression method using mucoadhesive polymers like manugel, acretamer 940 and gum cyamopsis in different ratios. The formulated buccal tablets were evaluated for drug-excipient incompatiblity, precompression parameters (angle of repose, bulk density, hausner's ratio etc.) and post compression parameters like hardness, friability, drug content uniformity and *In vitro* drug release. Among the 9 formulations, F1, F7 and F8 formulations containing 10mg Manugel, 10 mg and 20 mg Gum cyamopsis respectively were selected for swelling studies, bioadhesion studies and *ex vivo* permeation studies based on *invitro* drug release, they showed 96.35, 95.31and 93.48 respectively within 8 hrs. Hence, F1 formulation was optimized. All the 9 formulations showed good flow properties, hardness and friability. The drug release pattern of this formulation was found to be case-II non-fickian and approaching zero order kinetics. Short-term stability studies of the optimized formulation was carried out and there was no signigicant change in % drug release, drug content and bioadhesion values during 90 days (3 months) at 40±2ºC/75±5% RH.

KEYWORDS: Nitrendipine, Mucoadhesive buccal tablets, calciuum channel blocker, manugel, acretamer 940, gum cyamopsis, bioadhesion strength, swelling index and permeability coefficient.

INTRODUCTION

Among the various routes of drug delivery, oral route is the most suitable and most widely accepted by the patients for the delivery of therapeutically active drugs. But, after oral administration many drugs are subjected to presystemic clearance in liver, which often leads to lack of correlation between membrane permeability, absorption and bioavailability. Orotransmucosal drug delivery is an alternative approach to the systemic and enteral drug delivery. It avoids the drawbacks associated with the conventional route. Within the oral cavity sublingual region provides rapid onset of action as it is more permeable, thinner and considerable surface area and high flow of blood. But, the major drawback with this site is that it is very difficult to keep the dosage form in contact with the mucosa for sufficient time because it gets rapidly washed by saliva and tongue activity. The permeability when compared through different oral mucosa, sublingual route > buccal route > palatal. The buccal region of the oral cavity is an attractive target for administration of the drug of choice, particularly in overcoming deficiencies associated with the latter mode of administration. Moreover, rapid onset of action can be achieved relative to the oral route and the formulation can be removed if therapy is required to be discontinued.

Table: List of Ingredients

S.No	Materials	Category	Source
1	Nitrendipine	Anti hypertensive	Warner Laboratories pvt.ltd
2	Gum cyamopsis	Controlled release carrier	Merck Specialities pvt.ltd
3	Acritamer 940	Release modifying agent	Merck Specialities pvt.ltd
4	Manugel	Viscosity increasing agent	Merck Specialities pvt.ltd
5	Magnesium stearate	Lubricant	Merck Specialities pvt.ltd
6	Talc	Glidant	S.D Fine Chemicals, Boisar
7	Microcrystalline Cellulose	Diluent	Loba Chemie Pvt.Ltd

NITRENDIPINE (BP)[32,33]

Description: A calcium channel blocker with marked vasodilator action. It is an effective antihypertensive agent and differs from other calcium channel blockers in that it does not reduce glomerular filtration rate and is mildly natriuretic, rather than sodium retentive.

Category: Calcium Channel Blocker.

Dose: 20-40 mg/day

Absorption: Well absorbed

Protein Binding: > 99%

Metabolism: Hepatic metabolism

Excretion: Mechanism of action: By deforming the channel, inhibiting ion-control gating mechanisms, and/or interfering with the release of calcium from the sarcoplasmic reticulum, Nitrendipine inhibits the influx of extracellular calcium across the myocardial and vascular smooth muscle cell membranes The decrease in intracellular calcium inhibits the contractile processes of the myocardial smooth muscle cells, causing dilation of the coronary and systemic arteries, increased oxygen delivery to the myocardial tissue, decreased total peripheral resistance, decreased systemic blood pressure, and decreased afterload.

MICROMERITIC PROPERTIES[36,37]

Table: Acceptance Criteria of Flow Properties

S. No	Flow properties	Angle of repose(θ)	Compressibility Index (%)	Hausner ratio
1.	Excellent	25-30	<10	1.00-1.11
2.	Good	31-35	11-15	1.12-1.18
3.	Fair	36-40	16-20	1.19-1.25
4.	Passable	41-45	21-25	1.26-1.34
5.	Poor	46-55	26-31	1.35-1.45
6.	Very poor	56-65	32-37	1.46-1.59
7.	Very very poor	> 66	>38	>1.6

Drug-Excipients Compatibility Studies by FTIR

Excipients are integral components of almost all pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients, which are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation.

Infra-red spectroscopy is one of the most powerful analytical techniques to identify functional groups of a drug.

FTIR Studies

FTIR studies were performed on drug and the optimized formulation using FTIR. The samples were analyzed between wavenumbers 4000 and 400 cm^{-1}.

Differential Scanning Studies[38]

The results of DSC are displayed as thermal analysis curve in which the instrument signal is plotted against temperature or time. Analysis of thermal analysis curve is carried out using the instrumental software. DSC offered a rapid route to the determination of the extent of conversion. The concept underlying the technique is simple enough to obtain information on thermal changes in a sample by heating or cooling it alongside an inert reference.

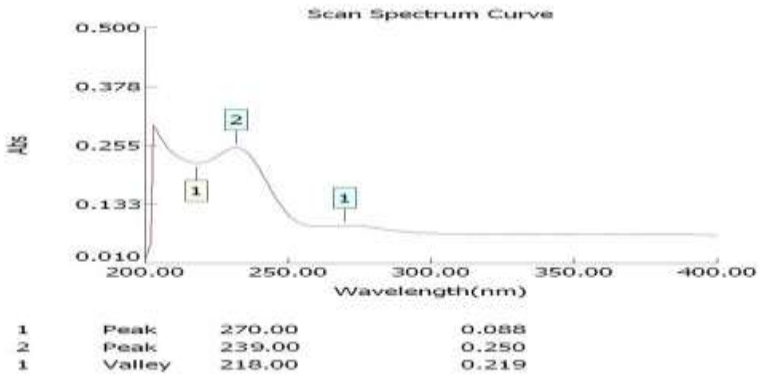
Table:Formulation of Nitrendipine Buccal Tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug (mg)	20	20	20	20	20	20	20	20	20
Manugel (mg)	10	20	30	-	-	-	-	-	-
Acritamer 940 (mg)	-	-	-	10	20	30	-	-	-
Gum cyamopsis (mg)	-	-	-	-	-	-	10	20	30
MCC pH 102 (mg)	66	56	46	66	56	46	66	56	46
Mg. Stearate (mg)	2	2	2	2	2	2	2	2	2
Talc (mg)	2	2	2	2	2	2	2	2	2
Total Weight (mg)	100	100	100	100	100	100	100	100	100

Analytical Method Development

Determination of absorption maxima.

10mg of pure drug was dissolved in 10ml of Methanol (stock solution). 1ml of above solution was taken and made up to10ml by using pH 6.8 phosphate buffer (100µg/ml).From this 1ml was taken and made up to 10 ml of pH 6.8 phosphate buffer (10µg/ml) and the solution was scanned in the range of 200-400 nm.



Standard graph in phosphate buffer pH 6.8 at 239 nm

Standard graph of Nitrendipine was plotted as per the procedure in experimental method and its linearity is analyzed**.** The standard graph of Nitrendipine showed good linearity with R^2 of 0.998, which indicates that it obeys "Beer- Lamberts" law.

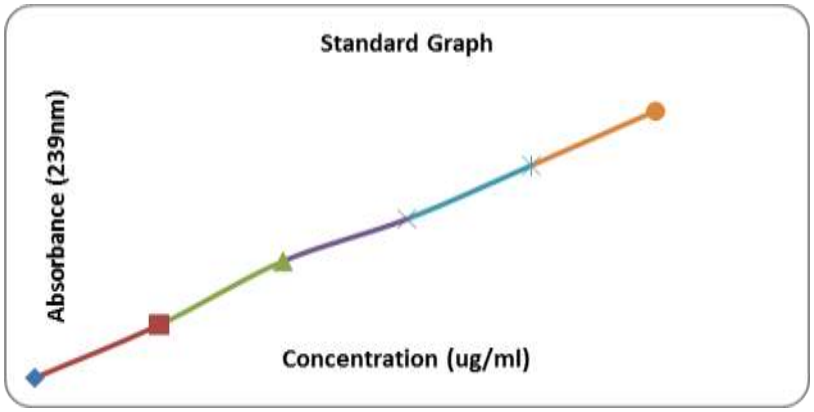


Fig: Standard graph of Nitrendipine in pH 6.8 phosphate buffer

Evaluation of Nitrendipine Tablets[36,37]

1. Friability test

The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (W) and transferred in to the friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W) final. The % friability was then calculated by

%F = initial weight—final weight/initial weight x 100

2. Weight variation test

Ten tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation is allowed in the weight of tablet by U.S. Pharmacopoeia.

Table: I.P limits for weight variation

Standard limit value in weight variation test Average Weight of a tablet	Percentage Deviation
130mg or less	±10
>130mg and <324mg	±7.5
324mg or more	±5.0

3. Drug content

Six tablets of each formulation were taken and amount of drug present in each tablet was determined. Powder drug equivalent to one tablet (100mg) 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 239 nm using pH6.8 phosphate buffer.

4. *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 900 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 10 hrs and analyzed after appropriate dilution by using UV Spectrophotometer at 239 nm.

5. *In vitro* bioadhesion strength

Bioadhesion strength of tablets were evaluated using a microprocessor based on advanced force gauge equipped with a motorized test stand according to method describe as it is fitted with 25kg load cell, in this test porcine membrane was secured tightly to a circular stainless steel adaptor and the buccal 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 buccal mucosa and the tablet immediately brought in contact with the mucosa. At the end of the contact time, upper support was withdrawn at 0.5mm/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.

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

6. Swelling Studies

Buccal tablets were weighed individually (designated as W_1) and placed separately in Petri dishes containing 15 mL of phosphate buffer (pH 6.8) solution. At regular intervals (0.5, 1, 2, 3, 4, 5, 6, 7 and 8hr), the buccal tablets were removed from the Petri dishes 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**.**

$$\text{Swelling index} = \frac{W_2 - W_1}{W_1} \times 100$$

7. *Ex-vivo* permeation studies through porcine buccal mucosa[39]

Ex vivo permeation study of Nitrendipine buccal tablets through the Pig buccal mucosa was performed using Franz-type diffusion cell. The freshly excised Pig buccal mucosal membrane was clamped between donor and receiver chambers of the Franz-type diffusion cell, facing the mucosal side towards the donor compartment. The receiver chamber was filled with fresh pH 6.8 buffer solution and after the buccal membrane was equilibrated for 30 min. The buccal tablet was placed in donor chamber and 1mL of buffer solution (pH 6.8) was added and the receptor compartment was maintained at 37±0.2^{0}C and continuously stirred at 50 rpm throughout the study. Aliquots (5mL) were collected at predetermined time intervals and filtered through a filter paper, and the amount of drug permeated through the buccal mucosa was then determined by measuring the absorbance at 239 nm using a UV spectrophotometer. The medium of the same volume (2mL), which was pre warmed at 37°C, was then replaced into the receiver chamber. The experiments were performed in triplicate (n = 3) and mean value was used to calculate the flux (J) and permeability coefficient (P).

J = (dQ/dt)/A;

P = (dQ/dt)/ ΔCA

RESULTS AND DISCUSSION

Table: Physical properties of pre-compression blend

Formulation Code	Angle of repose (Θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's Index (%)	Hausner's ratio
F1	25.10°	0.52	0.60	13.33	1.15
F2	25.43°	0.52	0.62	16.12	1.19
F3	25.41°	0.50	0.59	15.25	1.18
F4	26.40°	0.53	0.62	14.51	1.16
F5	27.12°	0.56	0.64	12.50	1.14
F6	25.31°	0.58	0.68	14.70	1.17
F7	26.11°	0.55	0.64	14.06	1.16
F8	26.15°	0.52	0.59	11.86	1.13
F9	26.10°	0.53	0.62	14.51	1.16

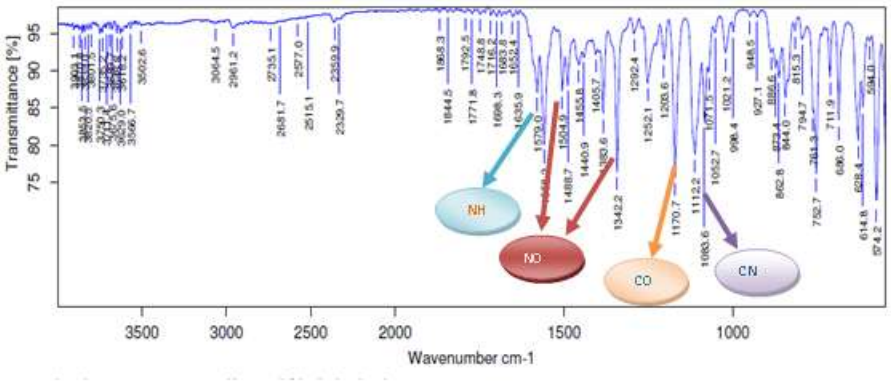


Fig.: FTIR Peak of Pure drug

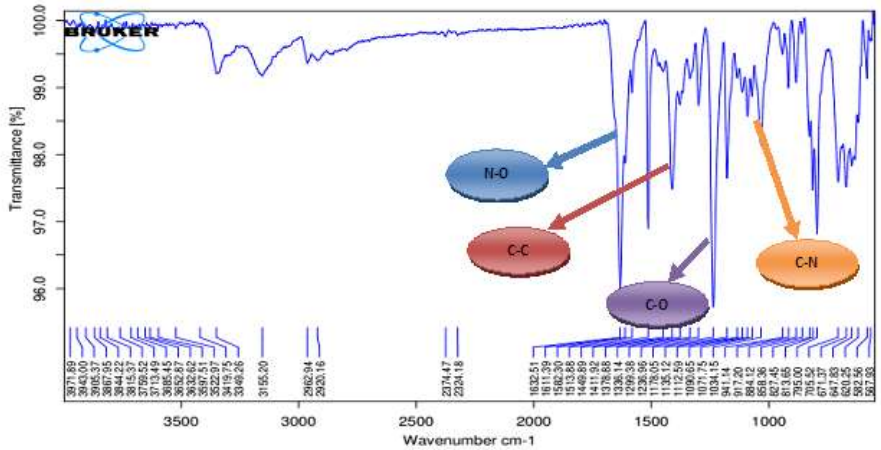


Fig.: FTIR Peak of Formulation

Differential Scanning Calorimertry of Pure Drug and Formulation

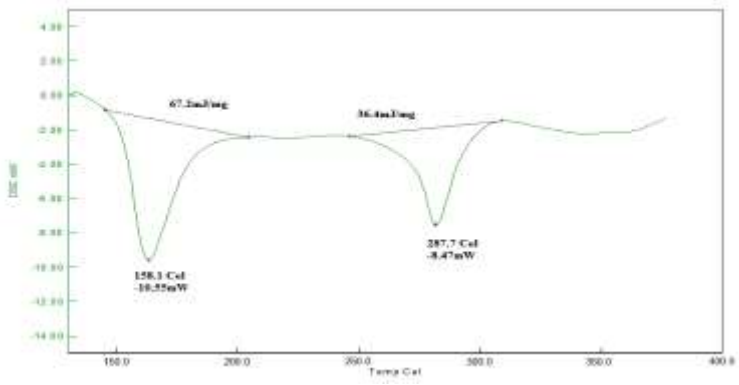


Fig. DSC of Formulation

DISCUSSION

Drug – Excipient Compatability Studies

It was observed that there is no significant change between the formulation and pure drug. So it indicates that is no the drug is thermodynamically stable.

Evaluation Tests for Various Formulations

Table: Post compression evaluation of Nitrendipine buccal tablets

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Content uniformity (%)
F1	Pass	2.76	3.6	0.43	96
F2	Pass	2.74	3.3	0.39	99
F3	Pass	2.71	3.0	0.38	98
F4	Pass	2.80	3.6	0.49	95
F5	Pass	2.81	3.9	0.52	97
F6	Pass	2.74	3.2	0.56	97
F7	Pass	2.76	3.1	0.53	99
F8	Pass	2.71	3.7	0.49	98
F9	Pass	2.73	3.2	0.48	95

***In-vitro* Drug Release Study**

Apparatus was set as per above conditions, one tablet was placed in each of the dissolution vessel and the dissolution test was started. After regular intervals of time the samples were collected i.e. 30 min, 1, 2, 3, 4, 5, 6, 7, 8 hrs and were analyzed using UV spectrophotometer at 239nm.

$$\% \text{ DR} = \frac{concentration\ X\ dissolution\ media\ volume\ (900ml)\ X\ dilution\ factor}{1000} X$$

Table: Comparative In-vitro Dissolution

TIME(Hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	21.24	15.47	13.86	5.9	4.13	2.62	19.84	15.46	12.48
1	29.17	23.41	20.14	12.6	10.49	5.88	28.46	24.69	21.51
2	39.42	31.68	29.44	19.85	17.27	12.49	33.47	32.63	29.84
3	51.49	39.89	33.41	26.32	23.65	19.67	48.62	44.81	38.41
4	60.94	46.53	37.86	33.11	29.41	23.14	56.51	51.73	47.31
5	72.34	57.16	46.7	40.12	36.28	29.63	69.48	63.42	59.14
6	81.66	64.91	52.49	48.29	41.92	34.22	81.47	71.69	66.82
7	91.44	71.22	59.33	52.64	46.33	40.19	89.35	84.52	71.43
8	96.35	80.18	64.81	59.17	50.18	44.66	95.31	93.48	82.14

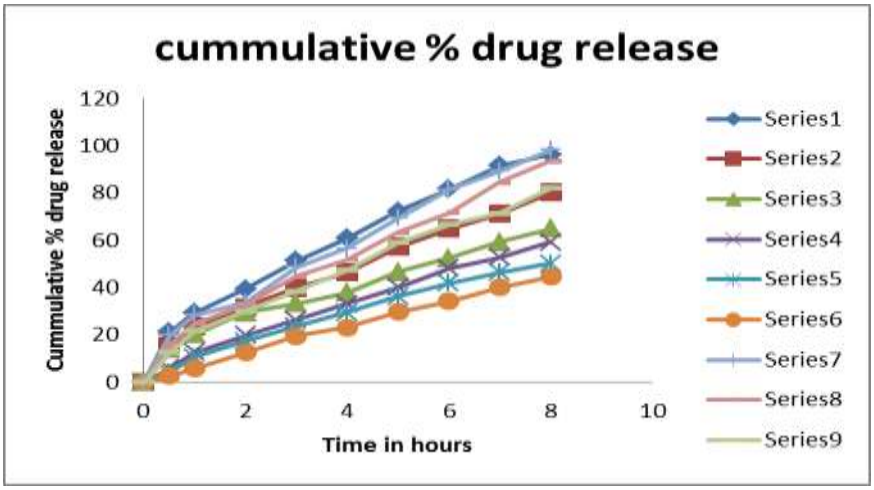


Fig: Dissolution Profile for F1-F9

DISCUSSION

From the dissolution studies, tablets containing Acritamer 940 was retards the drug release more than 8 hrs hence those formulations did not take into consideration. Formulations prepared with Manugel and Gum cyamopsis were shown good drug release in 8 hrs. F1, F7 and F8 formulations were shown maximum drug release at 8 hrs. Hence those formulations were selected as good formulations and those formulations were taken to perform Bioadhesion, Swelling index, Exvivo permeation studies.

In-vitro Bioadhesion Strength.

Table: Bioadhesion strength of selected formulations.

Formulation Code	Bioadhesion Strength	
	Peak Detachment Force (N)	Work of Adhesion (mJ)
F1	4.5	16.43
F7	4.5	15.24
F8	4.9	13.43

Discussion

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 F1.

Swelling Studies

Table: Swelling index of selected formulations

S.NO	Time (hrs)	F1	F7	F8
1	0.5	19.73	19.28	17.42
2	1	22.42	22.93	28.89
3	2	29.90	33.78	37.59
4	3	36.56	46.97	46.35
5	4	48.93	52.43	52.75
6	5	58.40	58.74	67.58
7	6	67.58	66.56	79.23
8	7	77.92	78.73	82.42
9	8	89.96	89.10	89.73

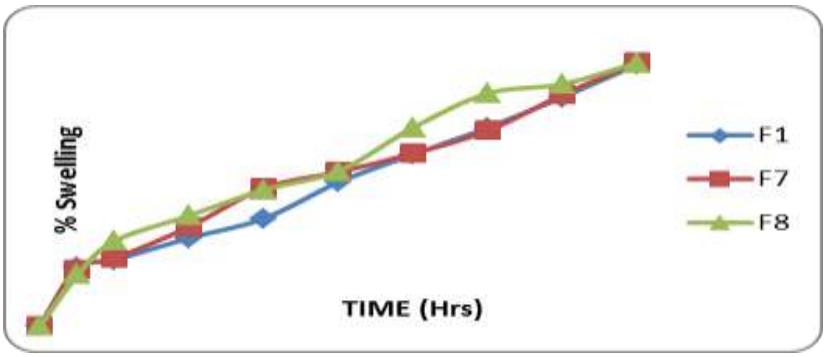


Fig: Swelling studies of Nitrendipineselected buccal tablets

DISCUSSION

The swelling studies were performed for the formulations which were shown desired drug release.

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

Table: *Ex vivo* permeation studies of selected formulations through porcine

S.No	Time (hrs)	F1	F7	F8
1	0.5	19.73	19.28	17.42
2	1	22.42	22.93	28.89
3	2	29.90	33.78	37.59
4	3	36.56	46.97	46.35
5	4	48.93	52.43	52.75
6	5	58.40	58.74	67.58
7	6	67.58	66.56	79.23
8	7	77.92	78.73	82.42
9	8	89.06	89.90	89.73
10	Flux ($\mu g.hrs^{-1}cm^{-2}$)	499.43	469.32	434.38
11	Permeability coefficient (cm/hr)	0.4994	0.2218	0.1525

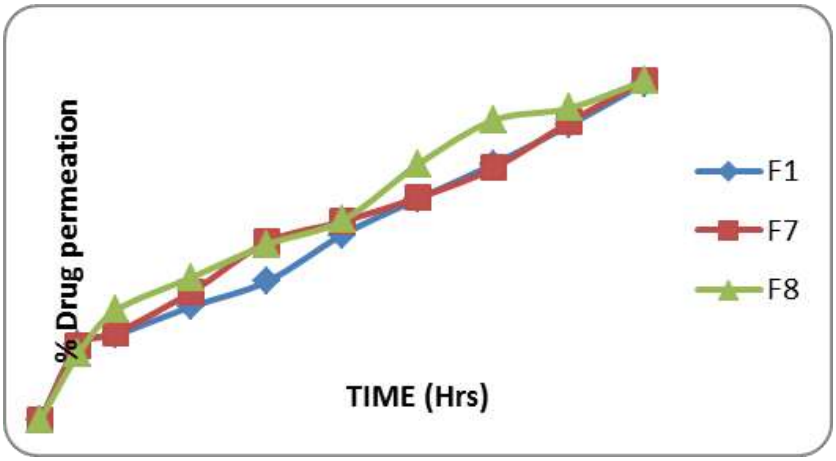


Fig : *Ex vivo* permeation studies graph of selected formulations through porcine buccal mucosa.

DISCUSSION

From the Table it was evident that selected formulations were showing good flux and permeability coefficient values. Among the selected formulations F1 formulation was showing maximum flux value of 499.43 ($\mu g.hrs^{-1}cm^{-2}$) and permeability coefficient value was 0.4994 (cm/hrs).

Kinetic Analysis of Dissolution Data of Optimised Formulation:

Zero order release rate kinetics

To study the zero–order release kinetics the release rate data are fitted to the following equation.

$F = K_o t$

First order release rate kinetics: The release rate data are fitted to the following equation

Log (100-F) = kt

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

F = k t1/2

In higuchi model, a plot of % drug release versus square root of time is linear.

Kors-meyer and Peppas release model

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$M_t / M_\infty = K t^n$

Table 4.3: Release kinetics

	ZERO	FIRST	HIGUCHI'S	PEPPAS
	%CDR vs T	Log % D.Remaining vs T	%CDR vs √T	Log C vs Log T
Slope	11.17	-0.157	34.62	0.559
Intercept	13.62	2.074	4.508	1.466
R^2	0.967	0.918	0.988	0.990

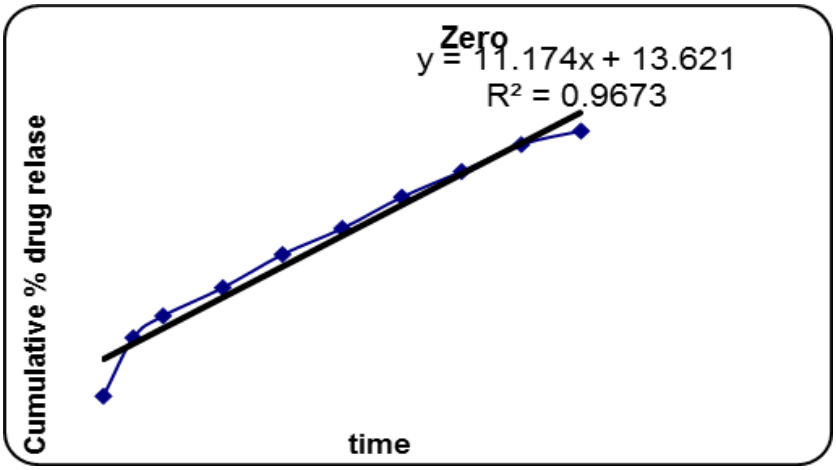


Fig 4.3.a: Zero order plot of optimized formulation

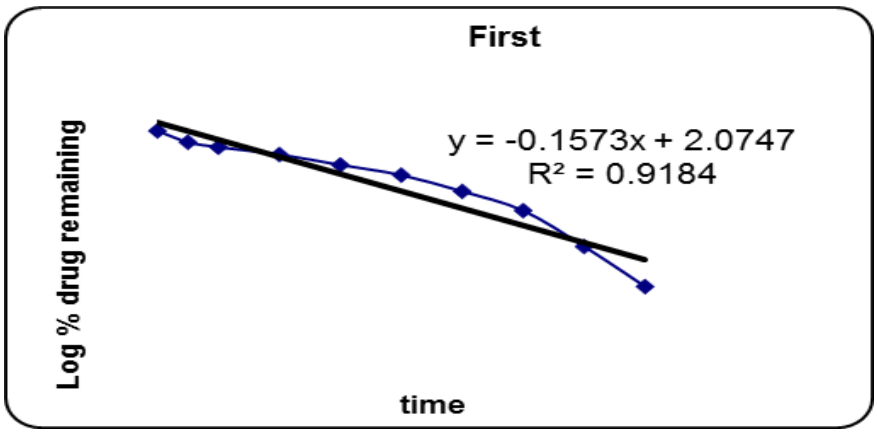


Fig 4.3.b: First order plot of optimized formulation

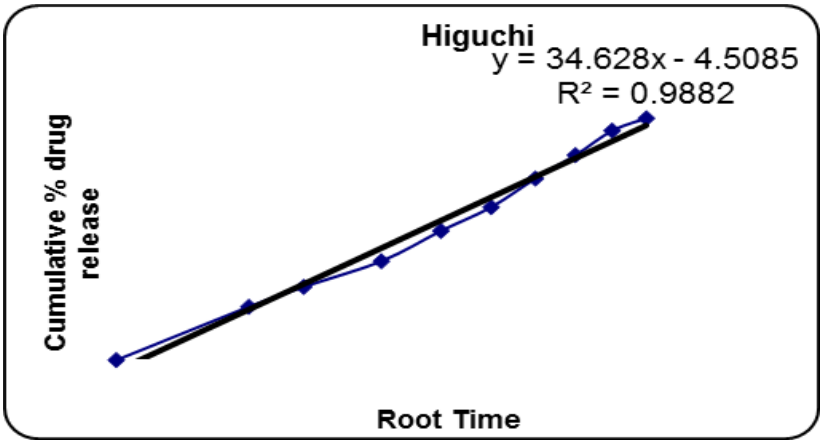


Fig 4.3.c: Higuchi plot of optimized formulation

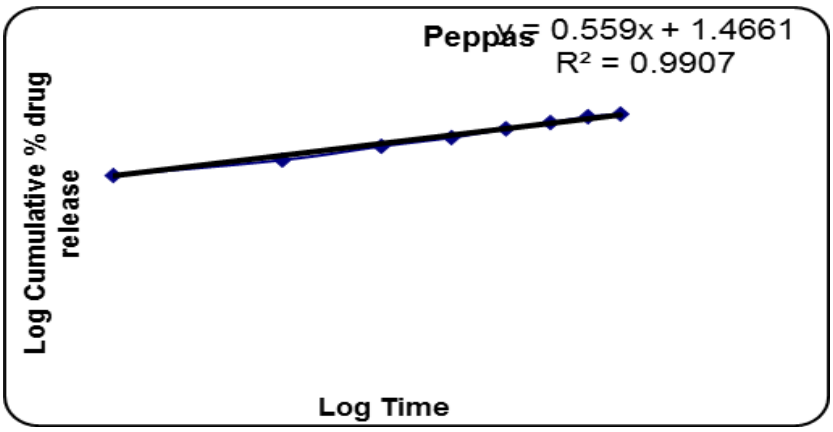


Fig 4.3.d: Kars mayer-peppas plot of optimized formulation.

DISCUSSION

Based on the all studies F1 formulation was found to be better when compared with all other formulations. This formulation was following Kars mayer peppas mechanism with regression value of 0.990.

Stability Studies

Formulation Code	% Drug Release Data				Drug Content	Bioadhesion Force
	1st day	30th day	60th day	90th day		
F1	96.35	96.20	96.15	96	99	16.05

DISCUSSION

Results from stability studies indicates that there were no significant changes in the optimized formulation F1 in % drug release, drug content and bioadhesion force during the storage period of three months at 40±2ºC/75±5%RH .

CONCLUSION

Among all the formulations F1 formulation containing 10mg manugel exhibited significant bioadhesive properties and permeation coefficient with optimum drug release i.e., 96.35% . The drug release pattern of this formulation was found to be non-fickian and approaching zero order kinetics. Short-term stability studies of the optimized formulation was carried out and there was no signigicant change in % drug release, drug content and bioadhesion values during 90 days (3 months) at 40±2ºC/75±5% RH.

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