FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL TABLET OF FENOFIBRATE.

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Abstract:-The aim of this work was to develop a tablet for the buccal delivery of the poorly water-soluble drug Fenofibrate which is a broad spectrum Fibric acid derivative used to reduce cholesterol levels in patients at risk of cardiovascular disease, for that an attempt was made to solubilize Fenofibrate by complexation with β- CD and then delivery via buccal mucosa. HPMC K4M and Carbopol 934P were selected as mucoadhesive polymers while Ethyl cellulose, as backing material. The complexation was studied by phase solubility method which indicates the formation of complex with 1:1 stoichiometry. The complexation was further characterized and studied by FTIR and DSC. Modification of the release for a poorly water-soluble drug, Fenofibrate, from hydrophilic matrices using cyclodextrin complexation was evaluated. The buccoadhesive tablets for the delivery of fenofibrate were prepared by 3^2 factorial designs by direct compression of HPMC K4M and Carbopol 934P. The tablets were evaluated for in vitro dissolution, surface pH, swelling study and mucoadhesive properties. The surface pH of all formulations was found to be within ±1 units of neutral pH hence these formulations should not cause any irritation in buccal cavity. Carbopol 934P showed superior bioadhesion properties compared to HPMC K4M. The in vitro release results demonstrated that drug is released by non-Fickian diffusion mechanism with zero order kinetics. From the drug release data, it was evident that formulation F2 (containing CP 15mg and HPMC K4M 20mg) has shown highly satisfactory values for dissolution parameters and has released approximatelt 98.53% drug in 6 hr. Hence, formulation F2 considered as the optimized buccal tablet containing Fenofibrate inclusion complex with β- CD for improved bioavailability.

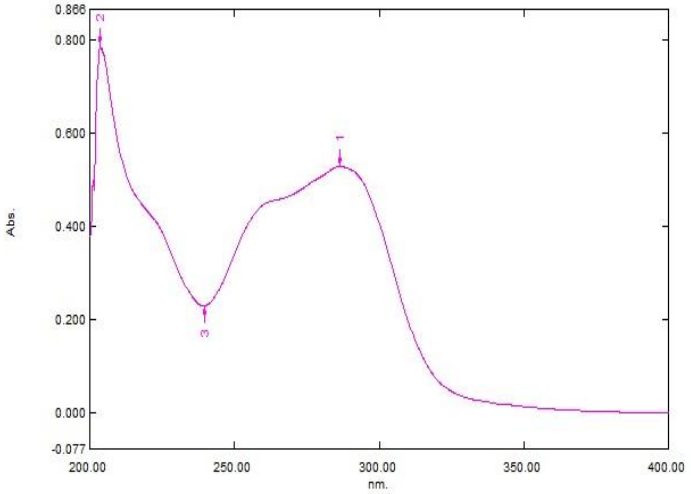
Keywords: Fenofibrate; β- Cyclodextrin; optimization; HPMC K4M; Carbopol 934P; Buccal delivery.

1. INTRODUCTION[1-3]

Baccal tissue is richly supplied with perfused blood capillaries hence this route has certain advantages such as; avoidance of irritation of the gastrointestinal membrane, relative permeability due to rich blood supply, reduced risk of overdose, non-invasive administration, ease of convenience and self-medication, improved patient compliance, higher bioavailability allowing lower doses, avoidance of liver or gastrointestinal metabolism, feasibility of beneficial adjunct to existing product and reduced risk of infectious disease transmission leading to the acceptance of buccal delivery as an alternative dosage form.

The buccoadhesive drug delivery systems have been developed basically to increase the retention of drug in the oral cavity. The route provides intimate contact between a dosage forms and absorbing tissue thereby resulting in high drug concentration in a local area and hence continuous release of drug from the medication towards medium from where it is constantly removed.

Fenofibrate is a BCS class II drug. It is mainly used to reduce cholesterol levels in patients at risk of cardiovascular disease. Like other fibrates, it reduces both low-density lipoprotein (LDL) and very low density lipoprotein (VLDL) levels, as well as increasing highdensity lipoprotein (HDL) levels and reducing triglycerides level. Fenofibrate increases the serum level of statins. Therefore, a lower dose of statin is generally necessary. Dose of fenofibrate must also be lowered in moderate to severe renal failure and most experts recommend that fenofibrate be given in the morning and the statin at night.



Fenofirate is practically insoluble in water (5.5µG/ml) and has high lipophilicity (log P = 5.24). Thus the dissolution rate of fenofibrate is expected to limit its absorption from the gastrointestinal tract.

The aim of this study was to prepare a new buccoadhesive tablet for poorly water-soluble drugs. Lipophilic drugs, although being well absorbed through oral epithelia, exhibit too low fluxes due chemical potential gradient, which is the driving force for transport.

In this regard, β-cyclodextrin have emerged as an effective tool to increase drug release rate of sparingly soluble drugs once incorporated in sustained-release matrix-type systems made of different polymers, β-cyclodextrin can affect some relevant properties of the drug delivery system that in turn are strictly related to drug release rate. Actually, β-cyclodextrin can promote changes in erosion rate and hydrophilicity of the matrix, induce osmotic effects, as well as modify drug effective mobility in the hydrated polymer. Also it is reported that cyclodextrin complexation of drug with β-cyclodextrin significantly increased the solubility of drug in the pH 6 phosphate buffer.

In this work, an attempt has been made to formulate buccoadhesive tablet of drug involving complexation of drug with β-cyclodextrin and preparation of tablets using hydrophilic polymer like HPMC and carbopol.

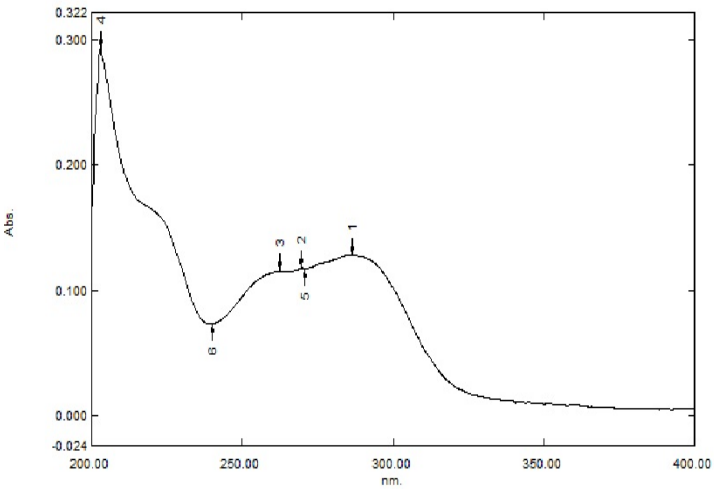
2. MATERIALS AND METHODS

Fenofibrate is gifted sample from Torrent research center, Ahmadabad. β- Cyclodextrin from Oxford Lab. Reagent, Mumbai. HPMC K4M and Carbopol 934P from SEVA Fine Chemicals, Ahmedabad.

2.1 Determination of UV Absorption Maxima (λmax) of fenofibrate

Stock solution (100µg/ml) of fenofibrate in methanol. This solution was appropriately diluted with phosphate buffer P^H 6.8 to obtain a concentration of 10µg/ml. The solution was kept in a fused silica cuvette 10 mm. The UV spectrum was recorded in the range of 200-400 nm on Shimadzu- 1800 double beam UV-visible spectrophotometer. The same procedure was carried out in methanol. The UV spectrum of fenofibrate indicated λmax in two different media is shown in Figure.

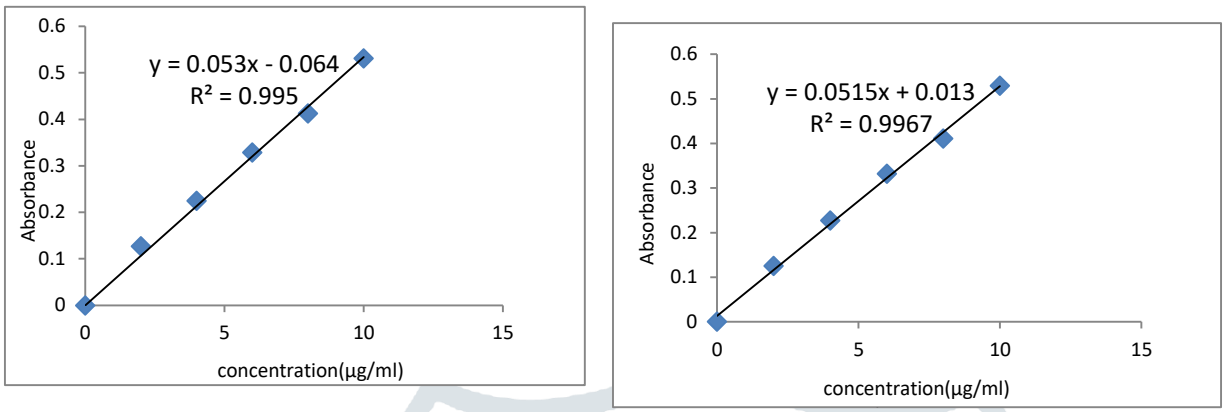
- λ max of Fenofibrate in both solvents are same **286nm**.



λmax in phosphate buffer P^H 6.8 **λmax in Methanol**

2.2 Preparation of Calibration Curve of fenofibrate

The standard curves of Fenofibrate in two solvent media i.e., P^H 6.8 Phosphate buffer and Methanol are shown in Figure.The graph of absorbance vs. concentration for Fenofibrate was found to be linear in the concentration range of 2-10 µg/ml at 286nm.

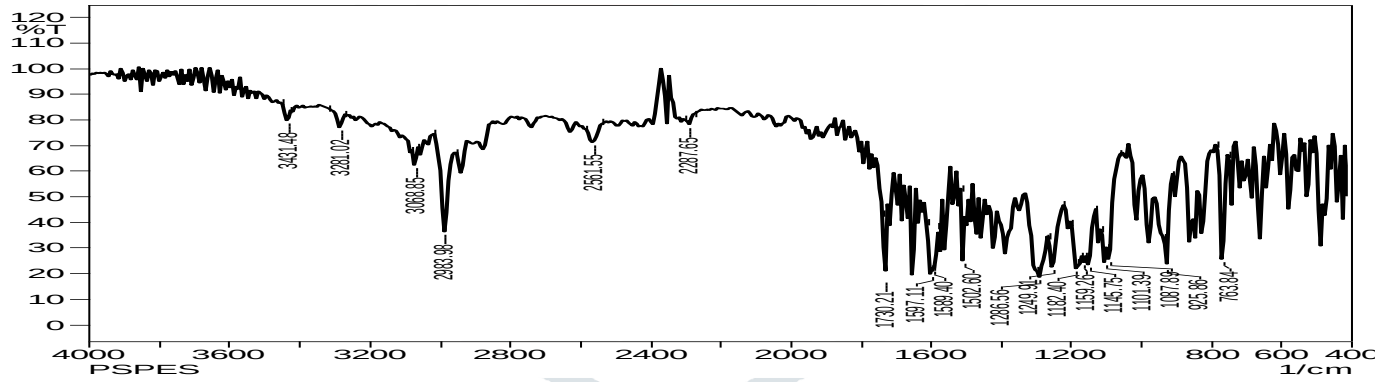


Calibration curve of fenofibrate in P^H 6.8 Phosphate buffer and Methanol

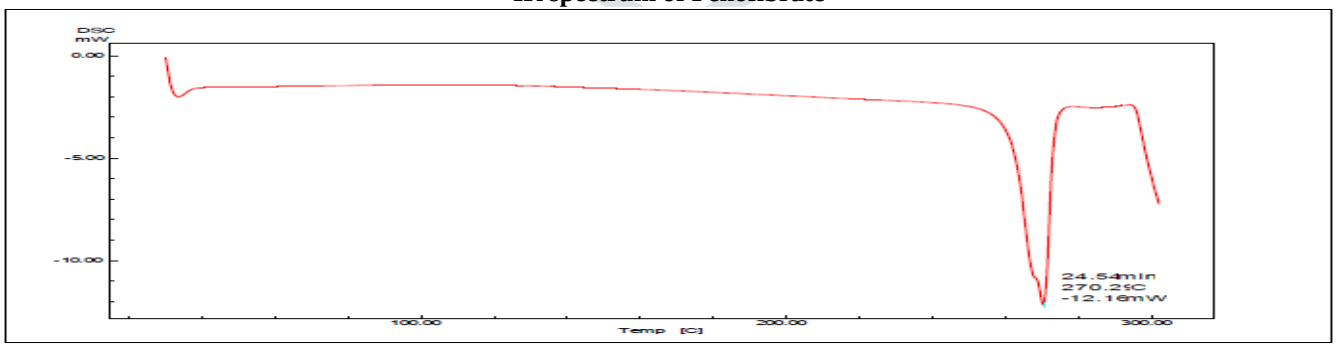
2.3 Preformulation Study

2.3.1 Determination of melting point: Melting point was determined by taking small amount fenofibrate in electrically operated digital melting point apparatus.

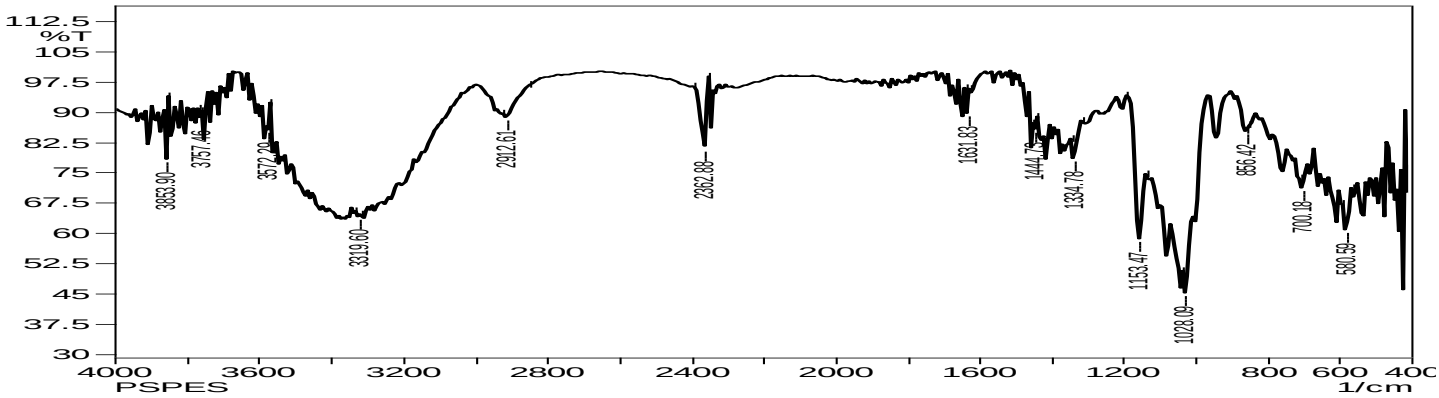
2.3.2 Drug Excipient Compatibility Study: The compatibility study of the fenofibrate with the selected excipients in physical mixture was checked out using FTIR spectrophotometer and DSC. The FTIR & DSC spectra of fenofibrate with the excipients are shown in Figure



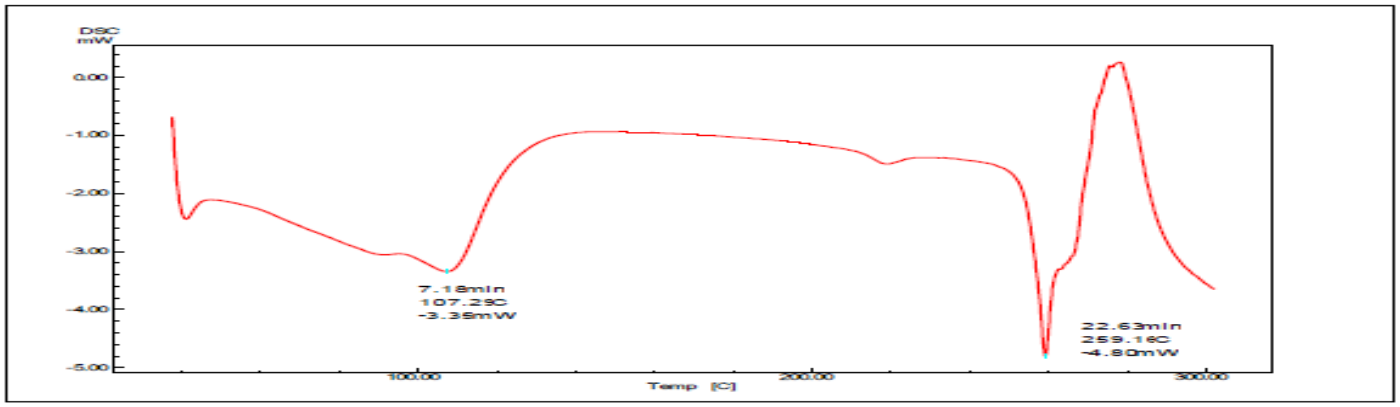
IR spectrum of Fenofibrate



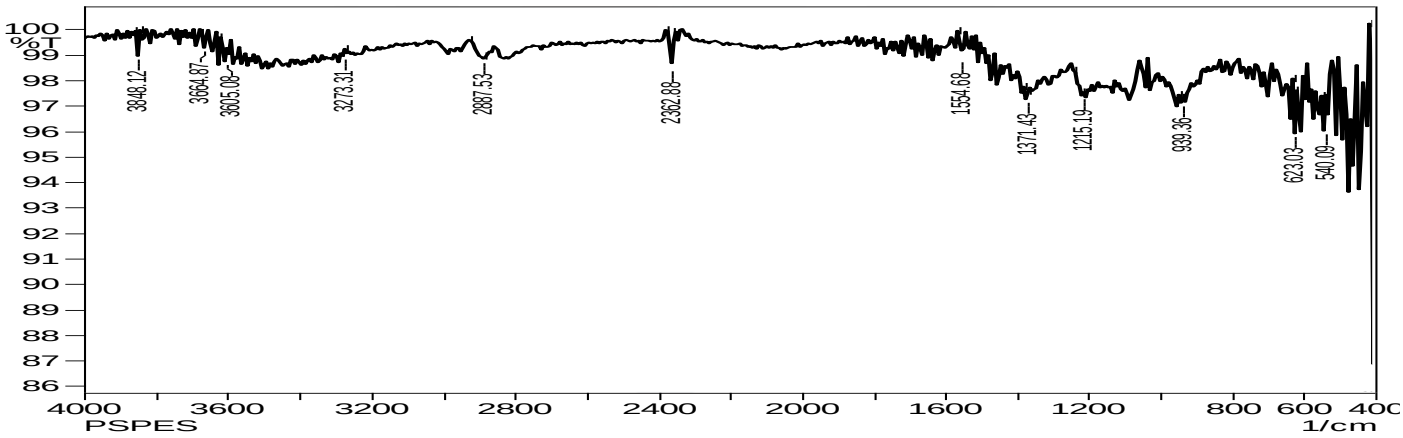
Differential Scanning Calorimetry of Fenofibrate



IR spectra of Fenofibrate and β-cyclodextrin complex



Differential Scanning Calorimetry for Drug- β-CD Complex



IR spectra for mixture of Drug, HPMC K4M and Carbopol 934P

2.4 Preparation of Fenofibrate buccoadhesive tablet [4]

2.4.1 Preparation of inclusion complexes of Fenofibrate with β-cyclodextrin in 1:1 molar ratio by Physical mixing, coprecipitation method

In this method, physical mixture were prepared by grinding known amounts of fenofibrate and β-CD in a mortal with pestle. In the co-precipitation method known amounts of β-CD and fenofibrate were dissolved in deionized water and methanol respectively. Both solutions were heated to 65^0C and mixed together. The final solution was continuously mixed at 65^0C and mixed together. The final solution was cooled to 5^0C and the crystals were separated by filteration through 0.45µm membrane filters. The product was dried and kept in desicator overnight to remove traces of solvents.

2.4.2 Preparation of tablet: In this work, direct compression method has been employed to prepare buccal tablet with HPMC K4M and Carbopol 934P as polymers. For one tablet accurately weighed 80 mg "Fenofibrate inclusion complex powder" which is equivalent to 40 mg of Fenofibrate was used in the formulation.

Procedure: All the ingredients including drug, polymer and excipients were weighed accurately according to the batch formulae. The drug is thoroughly mixed with mannitol on a butter paper with the help of a stainless steel spatula. Then all the ingredients except lubricant were mixed in the order of ascending weights and blended for 10 min in an inflated polyethylene pouch. After uniform mixing of ingredients, lubricant was added and again mixed for 2 min. The prepared blend (150 mg) of each formulation was pre-compressed on 10-station rotary tablet punching machine at low pressure to form single layered flat faced tablet of 8 mm diameter. Then, 50 mg of ethyl cellulose powder was added and final compression was done at a pressure of 4.5 kg/cm^2 to get the bilayer tablet.

Table-1:3^2 Factorial design formulations of Fenofibrate buccoadhesive tablet

Ingredients	Formulation								
	F_1 (mg)	F_2 (mg)	F_3 (mg)	F_4 (mg)	F_5 (mg)	F_6 (mg)	F_7 (mg)	F_8 (mg)	F_9 (mg)
Fenofibrate inclusion complex Powder	80	80	80	80	80	80	80	80	80
Carbopol 934P	10	15	20	10	15	20	10	15	20
HPMC K4M	20	20	20	30	30	30	40	40	40
Lactose DC	35.5	30.5	25.5	25.5	20.5	15.5	15.5	10.5	5.5
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
EC	50	50	50	50	50	50	50	50	50

2.5 EVALUATION

2.5.1 Evaluation of powder blend (ready for compression)

Angle of repose, bulk density, tapped density; Carr's index and Hausner's ratio was given from result.

2.5.2 Evaluation of Tablets

2.5.2.1 Tablet thickness:

Thickness of tablets was important for uniformity of tablet size. Thickness was measured using Vernier Calipers on 5 randomly selected samples.

2.5.2.2 Tablet hardness:

The resistance of tablet for shipping or breakage, under conditions of storage, transportation and handling, before usage, depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester.

2.5.2.3 Friability

Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that

revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined.

2.5.2.4 Weight variation

Twenty tablets were weighed individually and the average weight was determined. The % deviation was calculated and checked for weight variation as per IP.

2.5.2.5 Uniformity of the drug content:

Five tablets were powdered in a glass mortar and the powder equivalent to 4 mg of drug is placed in a stoppered 100 ml conical flask. The drug is extracted with 25 ml water with vigorous shaking on a mechanical gyratory shaker (100 rpm) for 2 hr and filtered into 50 ml volumetric flask through whatmann filter paper and more solvent is passed through the filter to produce 50 ml and analyzed for the drug content by measuring the absorbance at 286 nm against solvent blank.

2.5.2.6 Swelling index:

The swelling rate of the tablet is evaluated by using pH 6.8 phosphate buffer. The initial weight of tablet is determined (W_1). The tablet is placed in pH 6.8 phosphate buffer (6 ml) in a petridish placed in an incubator at 37 ± 1^oC and the tablet is removed at different time intervals (0.5, 1, 2, 3, 4, 5, 6, 7, 8 hr) blotted with filter paper and reweighted(W_2).

% Swelling index = $[(W_2-W_1)/W_1]$ x100.

2.5.2.7 Surface pH:

The surface pH of the tablets was determined in order to investigate the possibility of any side effects on the oral cavity. As acidic or alkaline pH is found to cause irritation to the buccal mucosa, hence attempt was made to keep the surface pH close to the neutral pH. A combined glass electrode is used for this purpose. Buccoadhesive tablets were left to swell for 2 hr on the surface of 1 ml of distilled water (pH 6.8±0.05) at room temperature. The surface pH was measured by means of electrode by bringing it into contact with the tablet surface and allowing to equilibrate for 1 min.

2.5.2.8 Mucoadhesive force [5-6]

The apparatus used for testing bioadhesion was assembled in the laboratory. Bioadhesive strength of the buccal tablets was measured on the "Modified Physical Balance Method" employing the method described by Gupta *et al* using bovine cheek pouch as model mucosal membrane. The method uses sheep buccal membrane as the model mucosal membrane.

A double beam physical balance was taken. The left pan was removed. To left arm of a balance, a thick thread of suitable length was hanged. To the bottom side of thread a glass stopper with uniform surface was tied. A clean glass mortar was placed below hanging glass stopper. In this, mortar was placed on a clean 500 ml glass beaker, within which another glass beaker of 50 ml capacity in inverted position was placed and weighed with 50 gm to prevent foating. The pan control system involves placing thermometer in 500 ml beaker and intermittently adding hot water in outer mortar filled with water. The balance so adjusted that, right hand side was exactly 5 gm heavier than the left

$$Bioadhesive\ force = \frac{mucoadhesive\ strength}{100}(9.81).$$

Mucoadhesive strength study of the formulations

Method: The balance adjusted as described above was used for the study. The bovine cheek pouch excised and washed was tied tightly with mucosal side upward using the thread over the base of inverted 50 ml glass beaker. This beaker suitably weighted was lowered into 500 ml beaker, which was then filled with isotonic phosphate buffer (pH 6.8) kept at 37ºC such that, the buffer reaches the surface of mucosal membrane & keeps it moist. This was then kept below left hand side of balance. The buccal tablet was then stuck to glass stopper through its backing membrane using an adhesive (feviquick). The 5gm on right hand side is removed. This causes application of 5 gm of pressure on buccal tablet overlying moist mucosa. The balance was kept in this position for 3 min and then slowly weights were increased on right pan, till tablet separates from mucosal membrane. The total weight on right pan minus 5 gm gives the force required to separate tablet from mucosa. This gives bioadhesive strength in grams. The mean value of three trials was taken for each set of formulations. After each measurement, the tissue was gently and thoroughly washed with isotonic phosphate buffer and left for 5 min before reading a new tablet of same formulation to get reproducible multiple results for the formulation.

2.5.2.9 *In vitro* drug release:

This is studied by using the USP XIII dissolution test apparatus (Electro Lab, TDT-08L) by using rotating basket at 37±0.5ºC at 100 rpm. Tablet is placed in 900 ml of phosphate buffer of 6.8 pH. Samples are withdrawn at specified time intervals (0.5, 1, 2, 3, 4, 5, 6, 7, 8 hr) and replaced with fresh dissolution medium (phosphate buffer pH 6.8). The amount of drug released is determined spectrophotometrically at 286 nm. The release rate study will be carried out for 8 hr.

3. RESULT AND DISCUSSION

3.1 Result of powder blend property

Table-2: Powder blend property of 3^2 factorial designs formulation F1 – F9

Sr. No.	Formulation	Angle of Repose(θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's Index	Hausner's ratio
1	**F1**	$24^0 6'$	0.584	0.650	12.40	1.11
2	**F2**	$25^0 6'$	0.570	0.680	19.29	1.19
3	**F3**	$27^0 12'$	0.580	0.684	19.29	1.17

4	**F4**	$22^0 12'$	0.568	0.649	14.26	1.14
5	**F5**	$23^0 12'$	0.581	0.686	17.24	1.18
6	**F6**	$25^0 38'$	0.570	0.647	14.28	1.13
7	**F7**	$24^0 18'$	0.583	0.650	11.87	1.11
8	**F8**	$22^0 30'$	0.891	0.660	12.67	1.04
9	**F9**	$25^0 42'$	0.570	0.648	14.03	1.13

3.2 Result of Hardness, Thickness, Friability, Avg.weight, Drug Content, Swelling Index, Surface pH

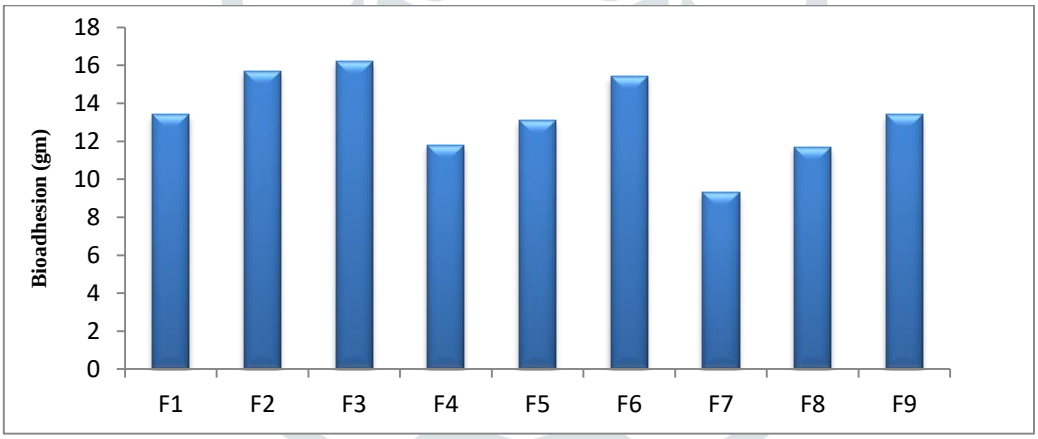
Table-3: post compression parameter of factorial batch formulation

Formulation code	Mean Hardness kg/cm^2	Thickness (mm)	Friability %w/w	Avg. weight (mg)	Mean Drug content (%)	Swelling index (%) after 6 hr.	Mucoadhesion (time of detachment hrs)	Tab. Surface pH
F1	4.50± 0.047	3.1	0.51	199.5± 1.08	99.52± 1.60	41.62%	>6	6.54
F2	4.55± 0.081	2.8	0.64	197.2± 0.68	98.12± 1.08	49.21%	>6	6.98
F3	4.32± 0.069	3.2	0.68	202.6± 1.14	94.9± 0.81	53.12%	>6	7.05
F4	4.41± 0.032	3.0	0.52	198.3± 1.24	95.77± 0.08	37.42%	>6	6.71
F5	4.29± 0.074	3.1	0.61	201.4± 1.39	101.14± 1.3	45.69%	>6	6.21
F6	4.51± 0.062	3.2	0.67	204.2± 0.94	98.44± 0.68	51.62%	>6	6.11
F7	4.39± 0.018	3.3	0.52	203.7± 1.55	96.09± 2.13	33.19%	>6	6.85
F8	4.42± 0.055	3.1	0.51	201.8± 1.70	97.09± 0.87	41.96%	>6	6.65
F9	4.33± 0.061	3.0	0.62	203.2± 0.62	96.33± 0.15	47.78%	>6	6.16

3.3 Result of Mucoadhesive Strength measurement

Table-4: Mucoadhesive Strength measurement for factorial batch.

FORMULATION CODE	MUCOADHESIVE STRENGTH (gm)	FORCE OF ADHESION (N)
F1	13.4	1.313
F2	15.7	1.538
F3	16.2	1.587
F4	11.8	1.156
F5	13.1	1.283
F6	15.4	1.509
F7	9.3	0.960
F8	11.7	1.146
F9	13.4	1.313



Bioadhesive strength measurement of Factorial design Formulations

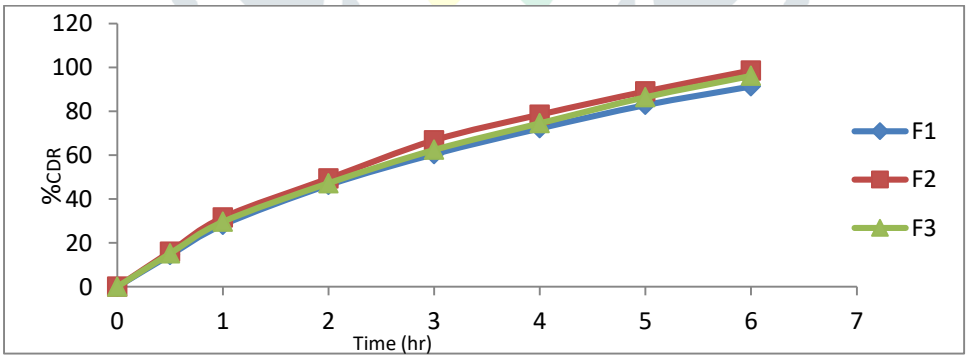
Increasing carbopol concentration increases the bioadhesion. This increase in the bioadhesion could be due to the formation of secondary mucoadhesive bonds with mucin because of rapid swelling and interpenetration of the polymer chains in the interfacial region, while other polymers undergo only superficial bioadhesion. The peak detachment force was considered to be dependent on the formation of hydrogen bonds between the functional groups of the bioadhesive and the mucus. HPMC alone had poor adhesive properties, but when used in combination with Carbopol, its overall adhesion was increased. Very strong bioadhesion could damage the epithelial lining of buccal mucosa.

3.5 Result of *in vitro* of drug release study

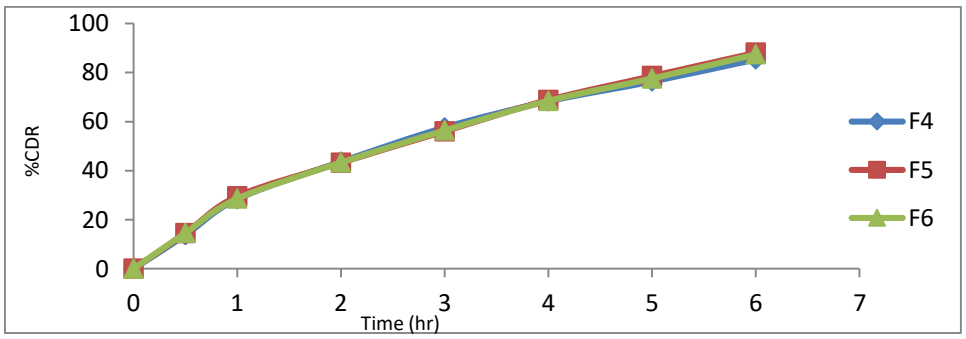
Table 5: % *in vitro* drug release profile of formulation F1 – F9

Time	Cumulative % Drug Release

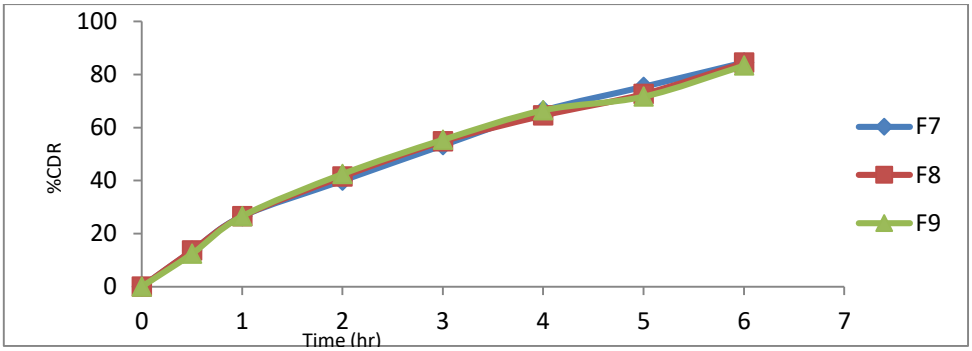
(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	14.46± 0.34	15.96± 0.77	15.19± 0.22	13.7± 0.40	14.4± 0.32	14.6± 0.44	13.4± 0.39	13.59± 0.37	12.4± 0.4
1	28.24± 0.16	31.57± 0.24	29.62± 0.39	28.42± 0.16	29.52± 0.28	28.6± 0.33	26.52± 0.25	26.51± 0.20	26.5± 0.26
2	46.40± 0.10	49.32± 0.34	47.23± 0.25	43.6± 0.27	43.2± 0.45	43.3± 0.45	39.9± 0.48	41.51± 0.33	42.4± 0.30
3	60.48± 0.27	66.74± 0.30	62.41± 0.10	57.6± 0.22	56.0± 0.32	56.4± 0.43	53.2± 0.5	54.78± 0.40	55.3± 0.36
4	72.20± 0.24	78.42± 0.24	74.54± 0.30	68.3± 0.32	68.8± 0.36	68.4± 0.39	66.3± 0.23	64.56± 0.13	66.5± 0.34
5	82.84±0.27	88.98± 0.7	86.44± 0.39	76.3± 0.39	78.5± 0.21	77.6± 0.22	75.3± 0.42	72.66± 0.25	71.6± 0.35
6	91.34±0.35	98.53± 0.44	96.15± 1.71	85.3± 0.29	88.0± 0.58	87.4± 0.4	84.5± 0.35	84.46± 0.43	83.3± 0.4



Cumulative percent drug released Vs time plots (zero order) of formulations F1, F2 and F3.



Cumulative percent drug released Vs time plots (zero order) of formulations F4, F5 and F6.



Cumulative percent drug released Vs time plots (zero order) of formulations F7, F8 and F9.

3.6 Kinetic Modeling and Mechanism of Drug Release

Dissolution profiles were fitted to various model and release data were analyzed on the basis of Korsmeyer Peppas equation, Zero order, First order and Higuchi kinetics.

Table-6: R^2, k values of release profile of each formulation made of formulation stage corresponding to Zero-order, First-order and Higuchi kinetics

Formulation Code	Zero order		First order		Higuchi's Equation	
	R^2	K_0	R^2	K_1	R^2	K_H
F1	0.964	14.83	0.973	0.171	0.955	35.45
F2	0.961	15.95	0.865	0.275	0.958	38.38
F3	0.969	15.53	0.917	0.219	0.953	36.89
F4	0.957	13.71	0.990	0.133	0.962	33.31
F5	0.966	14.04	0.948	0.154	0.959	33.82
F6	0.966	13.94	0.977	0.142	0.961	33.61
F7	0.972	13.63	0.984	0.133	0.950	32.23
F8	0.966	13.34	0.971	0.125	0.957	32.0
F9	0.957	13.30	0.983	0.121	0.955	32.03

R^2= coefficient of determination, k0=Zero-order release constant, k_1= First order release constant, K_H= Higuchi release constant.

Table-7: R^2, n, K_{KP} values of release profile of each formulation made of formulation stage corresponding to Korsmeyer Peppas kinetics

Batch no.	Korsmeyer Peppas			Mechanism of Drug release
	R^2	N	K_{KP}	
F1	0.996	**0.656**	**1.460**	**Non-Fickian**
F2	0.997	**0.641**	**1.503**	**Non-Fickian**
F3	0.998	**0.659**	**1.474**	**Non-Fickian**
F4	0.998	**0.616**	**1.456**	**Non-Fickian**
F5	0.998	**0.616**	**1.461**	**Non-Fickian**
F6	0.999	**0.626**	**1.453**	**Non-Fickian**
F7	0.998	**0.657**	**1.416**	**Non-Fickian**
F8	0.998	**0.638**	**1.425**	**Non-Fickian**
F9	0.996	**0.629**	**1.432**	**Non-Fickian**

Note-R^2 coefficient of determination, n= diffusional exponent, K_{KP}= Korsmeyer Peppas release constant.

CONCLUSION

The aim of this work was to be develop a tablet for the buccal delivery of the poorly water-soluble drug Fenofibrate, for that solubilization of Fenofibrate by complexation with β- Cyclodextrin and then delivery via buccal mucosa using Buccal tablets of Fenofibrate to release drug at mucosa site in unidirectional pattern for extended period of time without wash out of drug by saliva. HPMC K4M and carbopol 934P were selected as mucoadhesive polymers on the basis of their matrix forming properties and mucoadhesiveness while ethyl cellulose being hydrophobic as backing material.

Majority of designed Buccoadhesive tablets containing inclusion complex of Fenofibrate with β- CD displayed Zero order release kinetics, releasing 83-98.7% drug in 6 hr. The optimized formulations F2 containing HPMC K4M 20mg and Carbopol 934P 15mg exhibited zero order release kinetics with mucoadhesion time > 6 hr and SI 49.71 (after 6 hr) and released approximately 98.53 % drug in 6 hr. Hence, formulation F2 may be considered as the optimized buccal tablet containing Fenofibrate inclusion complex with β- CD for improved bioavailability.

A successful design of a buccal delivery system of poorly water soluble drug should guarantee both an intimate contact with the mucosa for an adequate time interval and proper release rates. Buccoadhesive tablets containing Fenofibrate inclusion complex with β- CD could therefore be of interest as a transmucosal

delivery system due to their recognized bioadhesive properties and the possibility of improving release features of drugs poorly soluble in aqueous media, which has been illustrated above. Overall evaluation of the mucoadhesive behavior of tablets shows good bioadhesive properties; although containing considerable amounts of β- CD and are suitable for transmucosal applications with proper release rates.

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