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DESIGN AND *IN VITRO* EVALUATION OF PROCHLORPERAZINE MALEATE BUCCOADHESIVE TABLETS AND COMPARISON OF MONOLAYER, BILAYER AND COMPRESSED COATED TABLETS

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Keywords:

Prochlorperazine maleate, Buccoadhesive, Non-fickian

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ABSTRACT: Buccoadhesive tablets have long been employed to improve the bioavailability of drugs undergoing significant first pass hepatic metabolism. Prochlorperazine maleate is an anti-emetic drug. It was under goes extensive first pass metabolism resulting in an oral bioavailability of 0 to 16 % and it shows variable absorption from GIT. Hence in the present work Buccoadhesive bilayered tablets of Prochlorperazine maleate were prepared with the objective of avoiding first pass metabolism and controlling the release of drug for prolog period of time. Controlled release buccoadhesive bilayered tablets containing Prochlorperazine Maleate was prepared using a 3^2 full factorial design. Amount of HPMC K4M CR and Carbopol 974 P NF were taken as the formulation variables (factors) for optimizing Bioadhesive strength and percentage release of drug. The bilayered buccoadhesive tablets were evaluated for Physical characterization, Assay, Swelling index, Adhesion study, *In-vitro* residence time, Microenvironment pH, *In-vitro* drug release and *In-vitro* permeation. The formulation with 5 mg HPMC and 7.5 mg Carbopol was consider as a best product with respect to Adhesive strength, in vitro residence time, in vitro drug release and in vitro permeation study. The drug release pattern of this formulation was found to be non-fickian and approaching zero order kinetics. This product was further subjected to stability study, the results of which indicated no significant change with respect to Adhesive strength, *in vitro* residence time, *in vitro* drug release and in vitro permeation study.

INTRODUCTION: Conventional dosage forms for delivery of drugs via the oral mucosa include solutions, erodible or chewable, buccal or sublingual tablets and capsules. Unfortunately, a major portion of the drug in these systems may be unavailable due to involuntary swallowing and a very short residence time, because of mastication, speech etc and hence sustained release is usually not within the scope of such formulations [1].

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In general, rapid absorption from these routes is observed because of the thin mucus membrane and rich blood supply. After absorption, drug is transported through the deep lingual vein or facial vein which then drains into the general circulation via the jugular vein, bypassing the liver and thereby sparing the drug from first-pass metabolism [1, 2].

Drugs can be absorbed from the oral cavity through the oral mucosa either by sublingual or buccal route [1]. Absorption of therapeutic agents from these routes overcomes premature drug degradation within the gastrointestinal tract as well as active drug loss due to first-pass hepatic metabolism that may be associated with oral route of administration[3].

Mucosa as a site of drug absorption: [1, 4] The oral mucosa can be divided into two general regions, the outer vestibule and the oral cavity. The vestibule is bounded on the outside by the lips and cheeks and on the inside by the upper and lower dental arches. The oral cavity is situated within the dental arches framed on the top by the hard and soft palates and on the bottom by the tongue and floor of the mouth. The oral mucosa consists of an outermost layer of stratified squamous epithelium, below which lies a basement membrane, and below this, in turn, a lamina propria and submucosa.

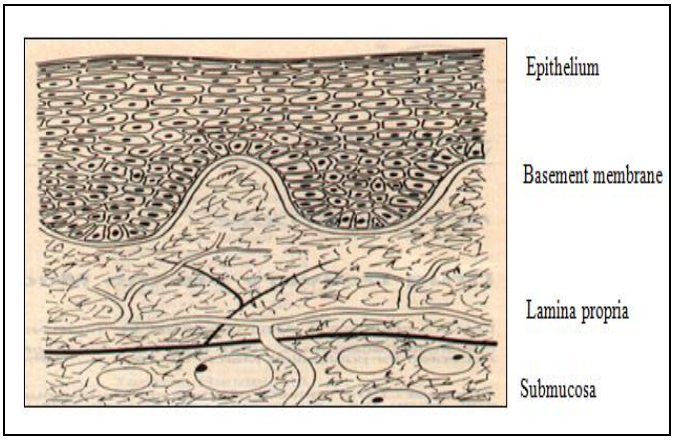

FIG. 1: SCHEMATIC DIAGRAM OF THE ORAL MUCOSA [5]

The oral mucosa can be distinguished according to five major regions in the oral cavity [6]:

- The floor of the mouth (sublingual region)
- The buccal mucosa (cheeks)
- The gum (ginigiva)

TABLE 1: AVERAGE EPITHELIAL THICKNESS OF ORAL MUCOSA [3]

Tissue	Structure	Epithelial thickness (µm)	Blood Flow ($ml.min^{-1}.cm^{-2}$)
Buccal	Non-keratinized	500-600	2.40
Sublingual	non-keratinized	100-200	0.97
Gingival	keratinized	200	1.47
Palatal	keratinized	250	0.89

Theories of Bioadhesion: [1, 4, 8]

- The Fracture Theory,
- The Diffusion Theory,
- The Wetting Theory,
- The Adsorption Theory,
- The Electronic Theory.

Mechanism of buccal absorption: [6, 7] The mechanisms by which drugs cross biologic lipid membranes are passive diffusion, facilitated diffusion, active transport and pinocytosis. Among these, majority of drugs move across oral mucosa by passive mechanism which is governed by the laws of diffusion.

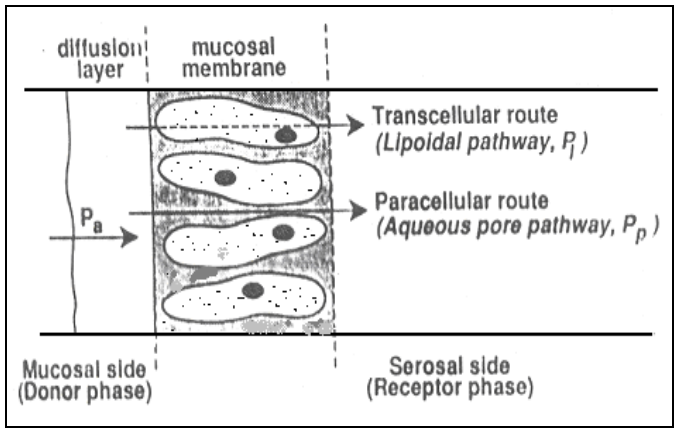

FIG. 2: TRANS-MEMBRANE PERMEATION ACROSS A MUCOSAL MEMBRANE

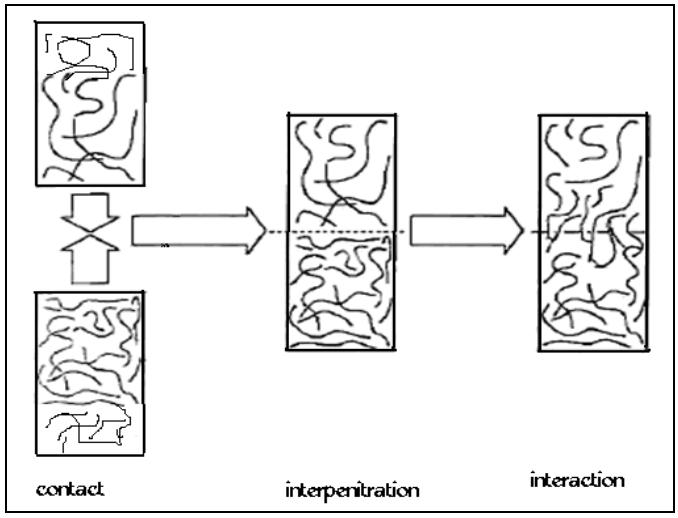

FIG. 3: SCHEMATIC PRESENTATION OF STEPS INVOLVED IN BIOADHESION [9]

Mucoadhesive Polymers: [1, 5, 6, 10] Mucoadhesive polymers are water soluble and water insoluble polymers which are swellable networks jointed by cross linking agents. The polymers should possess optional polarity to make sure it is sufficiently wetted by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place. An ideal polymer for a mucoadhesive drug delivery system should have the following characteristics.

TABLE 2: MUCOADHESIVE POLYMERS WITH THEIR MUCOADHESIVE PROPERTY [5]

Sr. no	Mucoadhesive property	Mucoadhesive Property
1	Carbopol 934	+++
2	Carboxymethylcellulose	+++
8	Gum karaya	++
9	Guar gum	++
10	Polyvinylpyrrolidone	+
12	Hydroxypropyl cellulose	+

Note: +++ excellent, ++ fair, +poor

Buccoadhesive tablet may be monolithic or bilaminated system. The main disadvantages of the monolayer tablet is the multidirectional release of the drug, hence some of the fraction of drug may swallowed. In order to avoid multidirectional release of the drug a bilaminated system was used. The Bilayered tablet made up of two layers, drug containing core layer and backing layer. The backing layer may be of water insoluble material like Ethyl cellulose or hydrogenated castor oil or may be polymeric coating layer which functioning as a adhesive and backing layer. A Mucoadhesive delivery system with a backing layer on one side can be used for local as well as systemic transmucosal drug delivery. Such a backing layer avoids sticking of the tablet to the finger during application in the oral cavity.[12]

Advantages of Mucoadhesive Buccal Drug Delivery Systems: [12]

1. Ease of administration.
2. Termination of therapy is easy.
3. Permits localization of drug to the oral cavity for a prolonged period of time.
4. Can be administered to unconscious patients.
5. Systemic absorption is rapid

Limitation of Buccal Drug Administration:

1. Drugs, which are unstable at buccal pH cannot be administered by this route.
2. Only drugs with small dose requirements can be administered.
3. Drugs may swallow with saliva and loses the advantages of buccal route.
4. Eating and drinking may become restricted.
5. Swallowing of the formulation by the patient may be possible.

Material: Materials used in the project, Prochlorperazine maleate was received as a gift sample, Amol Drug Parma Ltd. HPMC K4M CR, Carbapol 974P NF, Sucrose, PVP K/30, I.P.A, Mg. Stearate, Talc. Ethocel N 10, Lack of sunset yellow. All chemicals are of analytical grade and purchased from Merck Ind Limited Bangalore Karnataka India.

Method:

Determination of λ_{max}: The absorption maxima of Prochlorperazine maleate was determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer.

Procedure: Accurately weighed 25 mg of drug was dissolved in 500 ml of phosphate buffer in 500 ml amber colored volumetric flask with aid of sonication in bath sonicator for 20 min. This solution was labeled as stock-1. From the stock-120 ml of the solution were withdrawn and diluted up to 100 ml in 100 ml amber colored volumetric flask. The spectrum of this solution was run in 200-400nm range in U.V. Spectrophotometer (SCHIMADHZU). The Prochlorperazine maleate shows the absorbance maxima at 255nm. in phosphate buffer pH 6.8.

Uniformity of weight: The bilayered tablet was checked to ensure the proper weight of tablets is being made. Twenty tablets were selected as a random from each batch, weigh individually and the average weight was calculated. The batch passes the test for uniformity of the weight if not more than two of the individual tablet weight deviated from the average weight by more than the 10%.

Hardness: Hardness of the drug containing adhesive layer and bilayered tablet was measured using Hardness tester 8M (Dr. Schleunger). For each batch five tablets are tested.

Thickness: Five tablets were selected at random from each batch and thickness of adhesive layer and bilayered tablet was measured by using digital vernier calipers.

Drug content: The solution was protected from light throughout the assay. Weigh and powder 20 tablets. Weigh accurately a quantity of powder equivalent to 25 mg of Prochlorperazine maleate and extract with three quantities of, each of 10 ml, of ethanol containing 1% v/v of strong ammonia

solution. Filter the extract and to the combined extracts add sufficient ethanol to produce 100 ml. dilute 10 ml to 50 ml with ethanol and measured absorbance of the resulting solution at the maximum at about 258 nm. Calculate the contents of Prochlorperazine maleate taking 620 as the value of A (1%, 1cm) at the maximum at about 258nm.

Preparation of drug containing adhesive layer: Buccoadhesive bilayered tablet of Prochlorperazine maleate were prepared by wet granulation technique using different concentration of Hydroxypropyl methylcellulose (HPMC K4M CR premium) and Carbomer (Carbopol 974 P NF) in equal ratio. Prochlorperazine maleate, Sucrose, HPMC K4M CR Premium, and Carbopol 974P NF were passed through the sieve no. 60 and blended in glass mortar uniformly and granulated with polyvinyl pyrrolidone (PVP K30) in Isopropyl alcohol. The wet mass were passed through the sieve no. 20 and dried at room temperature in dark room for 5 min. and then in tray drier at 45^0C until the percentage moisture content goes below 1.5% w/w. the dried blend were passed through the sieve no. 30. The dried blend was weighed and the % yield was calculated. The dried granules were lubricated with magnesium stearate and talc passed through the sieve no. 60.

Bioadhesive Strength: Bioadhesive strength of the tablet was measured on the modified physical balance. The design used for measuring the bioadhesive strength was shown in figure. The apparatus consist of a modified double beam physical balance in which the right pan has been replaced by a glass slide with copper wire and additional weight, to make the right side weight equal with left side pan. A taflone block of 3.8 cm diameter and 2 cm height was fabricated with an upward potrution of 2 cm height and 1.5 cm diameter on one side. This was kept in beaker filled with phosphate buffer pH 6.8, which was then placed below right side of the balance.

$$\text{Bond strength (N/m}^2\text{)} = \frac{\text{Force of adhesion (N)}}{\text{Surface area of tablet (m}^2\text{)}}$$

Preparation of drug free backing layer: Granular grad of Ethyl cellulose (Ethocel N10) was mixed with the lack of sunset yellow colour passed through the sieve no 100 and mixed well.

Differential scanning Calorimetry: A differential scanning calorimeter was used for thermal analysis of drug and mixture of drug and excipients. The drug and excipients were passed through the sieve no. 60 and mixed in ratio as shown in **Table 15** the drug alone and mixture of drug and excipients was weighed directly in the pierced DSC aluminum pan (Aluminum Standard 40 ul) and scanned at the temperature range of 50-300 °C and at heating rate of 10 °C/min. and nitrogen purging rate 50 ml/min. the thermogram obtained were observed for any interaction.

***In vitro* drug release study:** *In vitro* drug release study of bilayer tablets were performed in automatic USP dissolution apparatus type 1 (basket). The dissolution tester USP (Elactrolab TDT-08L) was connected with Electro lab peristaltic pump, for automatic sample withdrawal and replacement of media, and Elactrolab fractional collector, for collection of sample. Phosphate buffer pH 6.8 was used as a dissolution media. The bowls of the dissolution tester was filled with 500ml of phosphate buffer pH 6.8 and allows to attaining a temperature of 37±0.5ºC. The reservoir for the replacement of the media was also filled with phosphate buffer. The collected samples were filtered through the 0.45 um mdi filter and absorbance of the solution was measured at 255 nm

Compression of bilayered tablet: Fifty mg of Drug containing adhesive layer and 40 mg of backing layer were weighed individually. The adhesive layer was compressed in 12 station rotary compression machine using 8mm (13/32 inches) flat surface punches at hardness of 2.5 to 3 Kp.

The backing layer was then added on the primarily compressed adhesive layer and compressed at a hardness of 5 to 6 kp.

Comparison of Buccoadhesive Tablets of Prochlorperazine Maleate: To justify the need of backing layer in buccal tablet, a mono layer tablet (without backing layer) and compressed coated tablet was prepared using the composition of optimized formulation (formulation SB3). The monolayer tablet and compressed coated tablet were evaluated for *in-vitro* drug release of monolayer and compressed coated tablet was compared with optimized bilayered tablets.

The results of adhesion strength, swelling index and dissolution profile.

Stability study: Stability testing of drug products begins as a part of drug discovery and ends with the demise of the compound or commercial product. FDA and ICH specifies the guidelines for stability testing of new drug products, as a technical requirement for the registration of pharmaceuticals for human use. The ICH Guidelines have established that long term stability testing should be done at 25^0C/60% RH; stress testing should be done at 40^0C/75%RH for 6 month.

RESULTS:

TABLE 3: COMPOSITION OF FORMULATION OF TRIAL SERIES

Ingredients	F0	F1	F2	F3	F4	F5	F6	F7	F8
Drug Containing Adhesive Layer									
Active	3	3	3	3	**3**	3	3	3	3
HPMC K4M CR	0.0	1.25	2.5	3.75	**5.0**	6.25	7.5	8.75	10
Carbpol 974P NF	0.0	1.25	2.5	3.75	**5.0**	6.25	7.5	8.75	10
Sucrose	45	42.5	40	37.5	**35**	32.5	30	27.5	25
PVP K/30	1.25	1.25	1.25	1.25	**1.25**	1.25	1.25	1.25	1.25
I.P.A	q.s	q.s	q.s	q.s	**q.s**	q.s	q.s	q.s	q.s
Mg. Stearate	0.25	0.25	0.25	0.25	**0.25**	0.25	0.25	0.25	0.25
Talc	0.5	0.5	0.5	0.5	**0.5**	0.5	0.5	0.5	0.5
Drug Free Backing Layer									
Ethocel N 10	39.6	39.6	39.6	39.6	**39.6**	39.6	39.6	39.6	39.6
sunset yellow	0.4	0.4	0.4	0.4	**0.4**	0.4	0.4	0.4	0.4

TABLE 4: ABSORBANCE OF PROCHLORPERAZINE MALEATE AT 255 nm

Conc. (µg/ml)	Absorbance			Average	S.D.
	Series 1	Series 2	Series 3		
2	0.107	0.117	0.126	0.117	0.010
4	0.211	0.228	0.219	0.219	0.009
6	0.317	0.333	0.324	0.325	0.008
8	0.427	0.414	0.431	0.424	0.009
10	0.541	0.544	0.537	0.541	0.004
12	0.645	0.652	0.65	0.649	0.004
14	0.754	0.766	0.764	0.761	0.006
16	0.854	0.855	0.874	0.861	0.011
18	0.965	0.973	0.988	0.975	0.012
20	1.071	1.088	1.091	1.083	0.011

TABLE 5: RESULTS OF PHYSICAL CHARACTERIZATION OF PREPARED BUCCOADHESIVE BILAYERED TABLETS OF TRIAL SERIES

Batch code	Weight(mg)		Hardness(Kp)		Thickness(mm)	
	Adhesive Layer	Total	Adhesive Layer	Total	Adhesive Layer	Total
F0	49.74 ±0.152	89.8(±0.332)	3.04(±0.15)	6.08(±0.22)	0.96(±0.034)	1.51(±0.024)
F1	49.78 (±0.084)	89.86(±0.39)	2.78(±0.19)	5.94(±0.114)	0.89(±0.019)	1.464(±0.04)
F2	49.8(±0.224	90(±0.2)	2.66(±0.207)	5.98(±0.239	0.916(±0.011)	1.51(±0.016)
F3	49.5(±0.339)	89.56(±0.371)	2.86(±0.167)	5.82(±0.148)	0.99(±0.019)	1.52(±0.008)
F4	50.1(±0.552)	89.38(±0.576)	3.06(±0.114)	5.96(±0.114)	0.91(±0.018)	1.42(±0.016)
F5	49.72(±0.249)	89.88(±0.319)	2.64(±0.134)	5.92(±0.164)	0.972(±0.008)	1.194(±0.011)
F6	49.94(±0.207)	89.74(±0.358)	2.88(±0.148)	6.08(±0.179)	0.986(±0.015)	1.51(±0.031)
F7	49.32(±0.377)	89.76(±0.404)	2.76(±0.152)	5.88(±0.084)	0.97(±0.034)	1.494(±0.04)
F8	49.62(±0.259)	89.52(±0.455)	2.54(±0.207)	5.94(±0.114)	0.956(±0.036)	1.52(±0.021)

TABLE 6: RESULTS OF THE ADHESIVE STRENGTH AND FORCE OF ADHESION

Batch no	Adhesive force in gm	Force of adhesion in Newton
F1	5.353(±0.46)	0.053(±0.005)
F2	8.939(±0.19)	0.088(±0.002)
F3	14.274(±0.3)	0.140(±0.003)
F4	19.93(±0.78)	0.236(±0.008)

F5	31.934(±0.45)	0.313(±0.004)
F6	40.12(±1.56)	0.394(±0.015)
F7	45.828(±0.45)	0.450(±0.004)
F8	51.436(±1.11)	0.505(±0.011)

TABLE 7: RESULTS OF DISSOLUTION PROFILE OF MONO, BILAYERED AND COMPRESSED COATED

Time (hr)	Batch no.		
	Mono layer	Bilayered	Compressed coated
0	0.00	0.00	0.00
1	37.69(±0.941)	14.99(±0.47)	8.93(±0.308)
2	48.5(±1.064)	27.82(±1.69)	14.41(±0.402)
3	57.57(±0.759)	37.41(±1.36)	23.82(±0.621)
4	74.91(±0.834)	49.23(±2.04)	39.54(±0.980)
6	90.42(±0.780)	66.51(±1.71)	68.45(±0.779)
8	94.42(±0.602)	91.92(±2.69)	85.29(±0.617)

TABLE 8: STABILITY STUDY OF OPTIMIZED BATCH AND CONTROL AT DIFFERENT TEMPERATURE

Time hr	Storage condition		
	Control	40° C / 75% RH	60° C
0.5	1.205(±0.02)	1.190(±0.03)	1.182(±0.02)
1	1.829(q0.04)	1.808(±0.02)	1.800(±0.04)
1.5	2.144(±0.04)	2.118(±0.03)	2.115(±0.05)
2	2.532(±0.05)	2.516(±0.04)	2.499(±0.05)
3	2.692(±0.04)	2.675(±0.04)	2.660(±0.03)
4	2.789(±0.06)	2.785(±0.04)	2.775(±0.02)
5	2.84(±0.05)	2.816(±0.05)	2.811(±0.05)
6	2.894(±0.05)	2.881(±0.06)	2.871(±0.02)

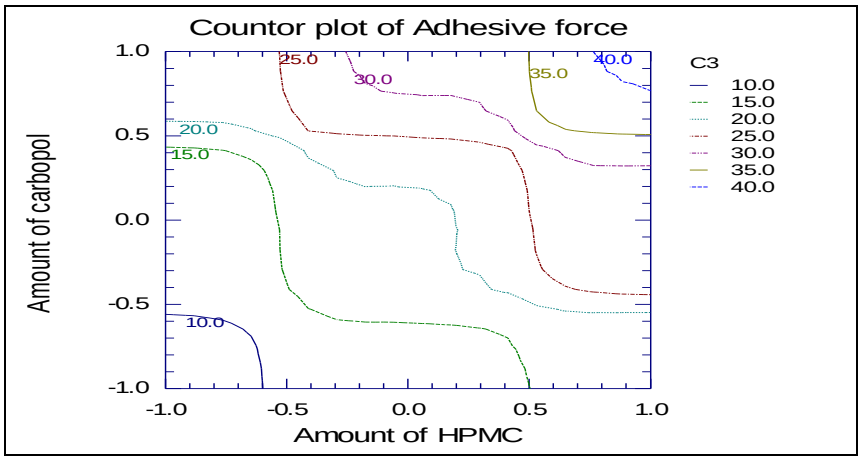

FIG. 4: CONTOUR PLOT OF THE VARIABLE RELEASE AT ADHESIVE STRENGTH

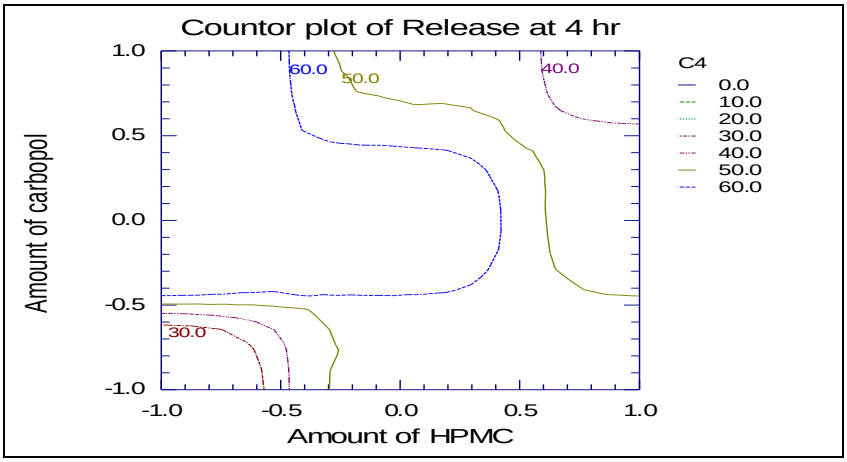

FIG. 5: CONTOUR PLOT OF RELEASE

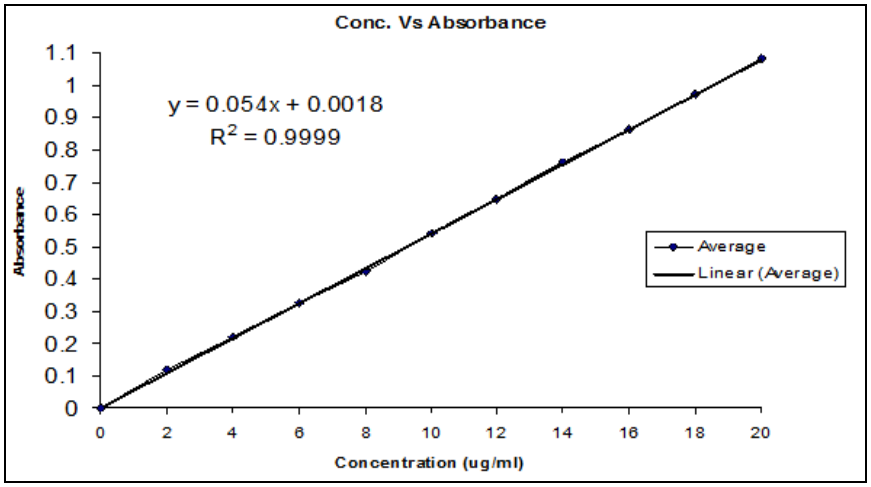

FIG. 6: LINEARITY CURVE OF PROCHLORPERAZINE MALEATE AT 255 nm

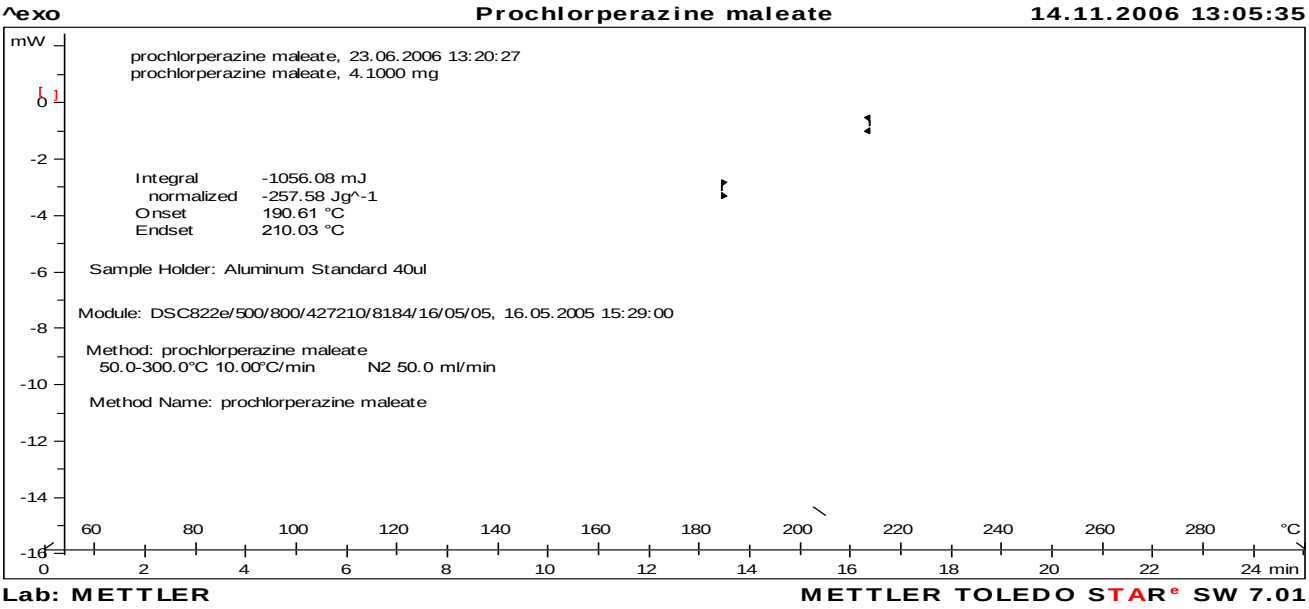

FIG.7: DSC THERMOGRAM OF PROCHLORPERAZINE MALEATE

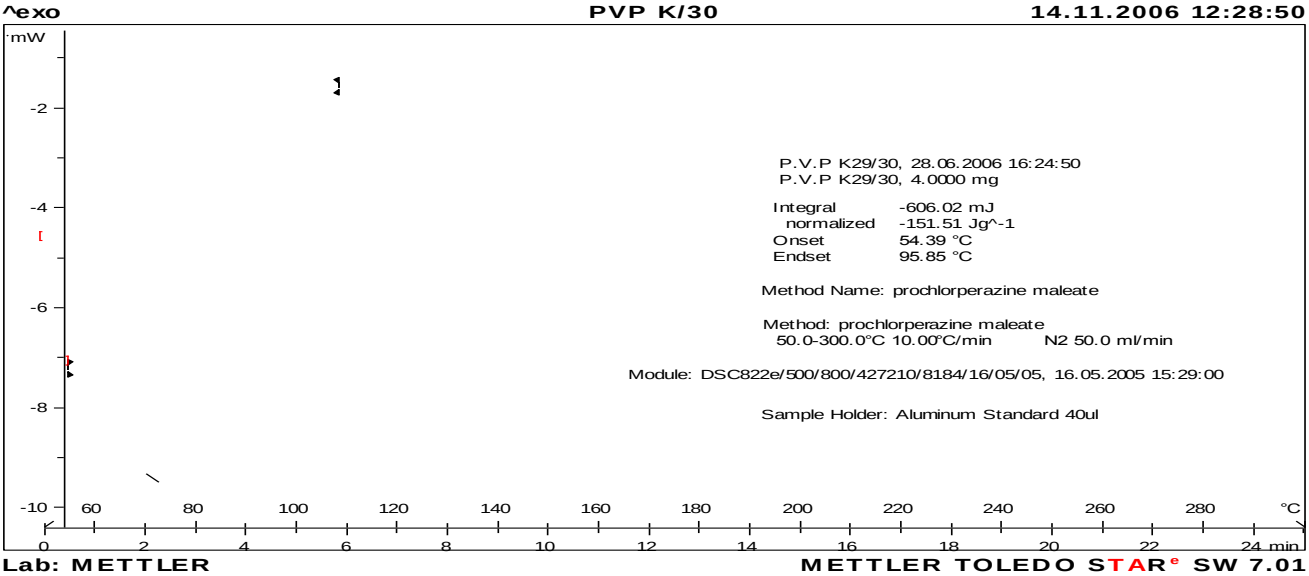

FIG. 8: DSC THERMOGRAM OF PVP K/30

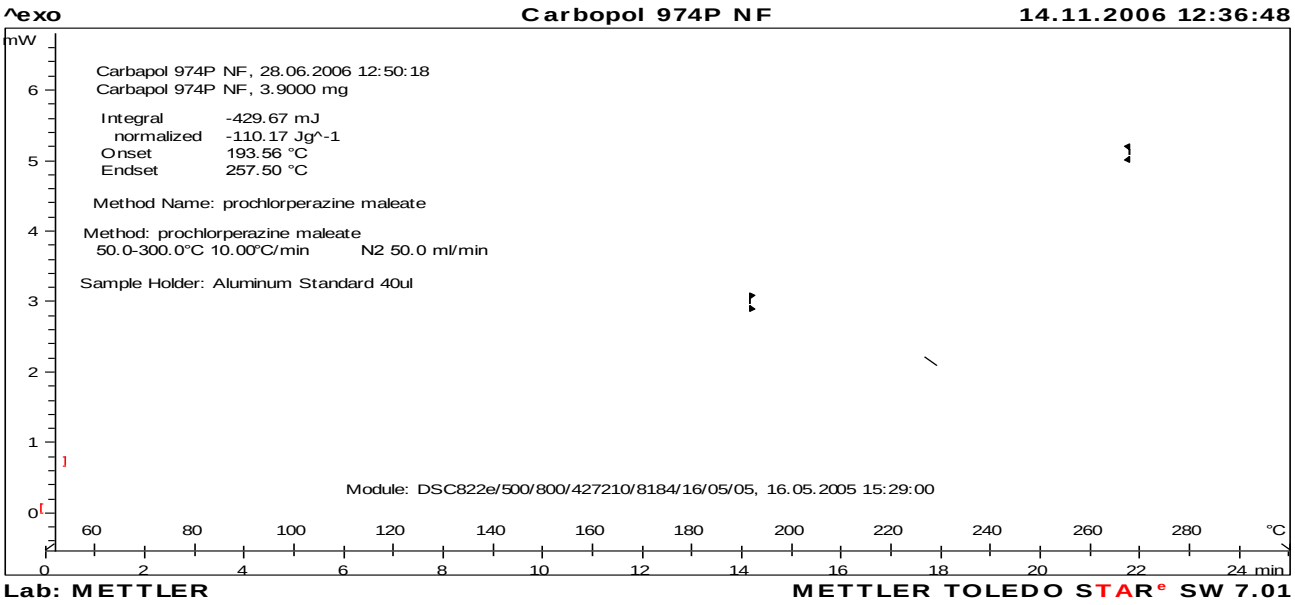

FIG. 9: DSC THERMOGRAM OF CARBOPOL 974 P NF

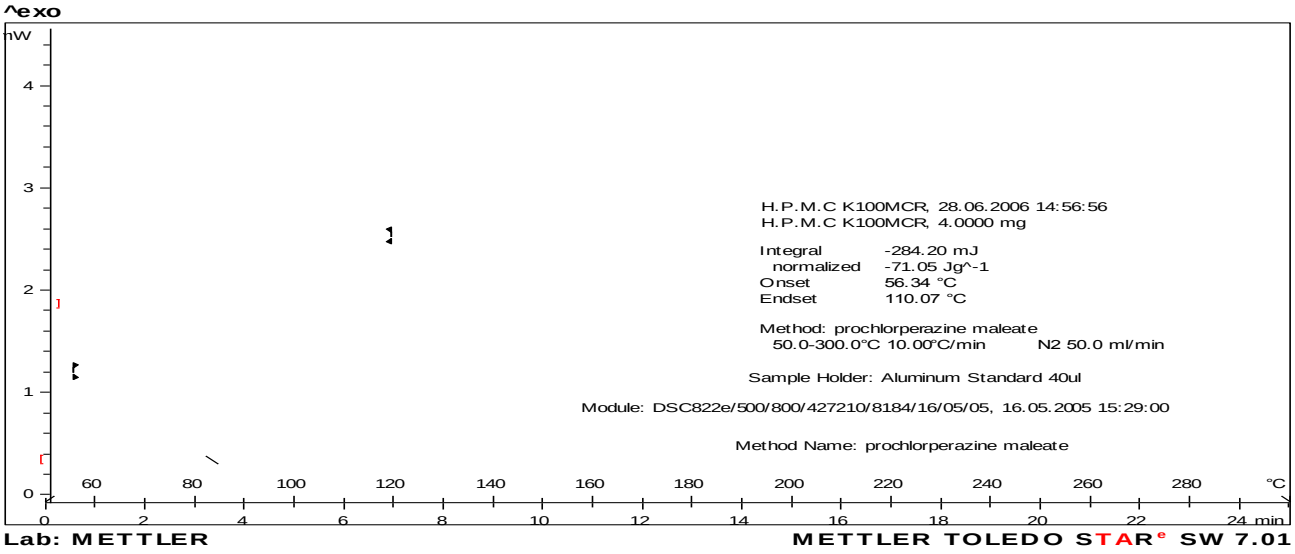

FIG. 10: DSC THERMOGRAM OF HPMC K4M CR

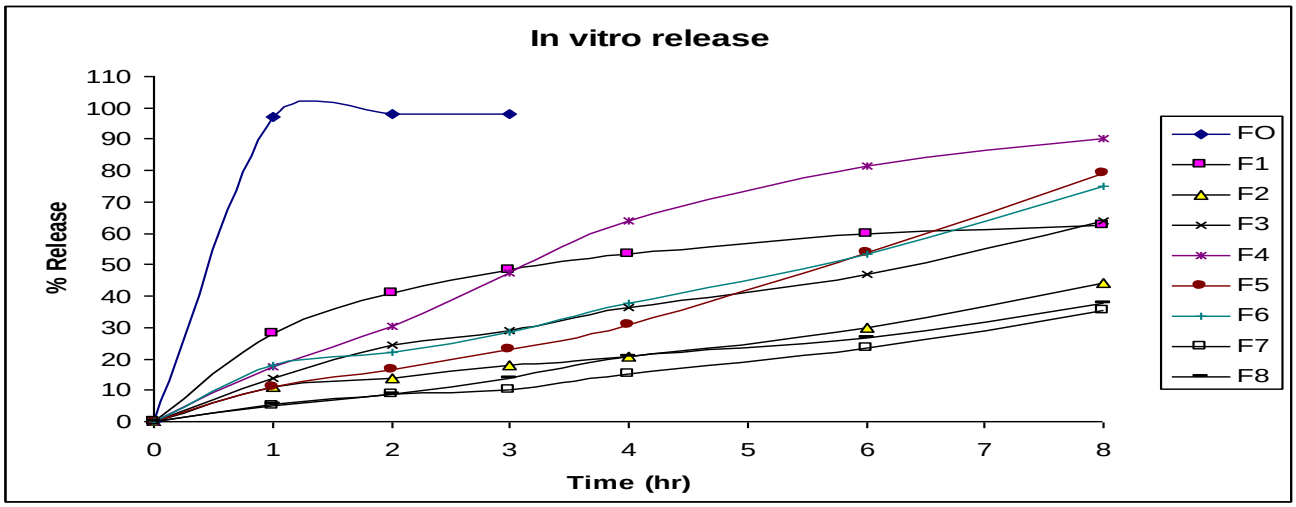

FIG. 11: PLOT OF CUMULATIVE PERCENTAGE RELEASE VERSUS TIME OF TRIAL SERIES

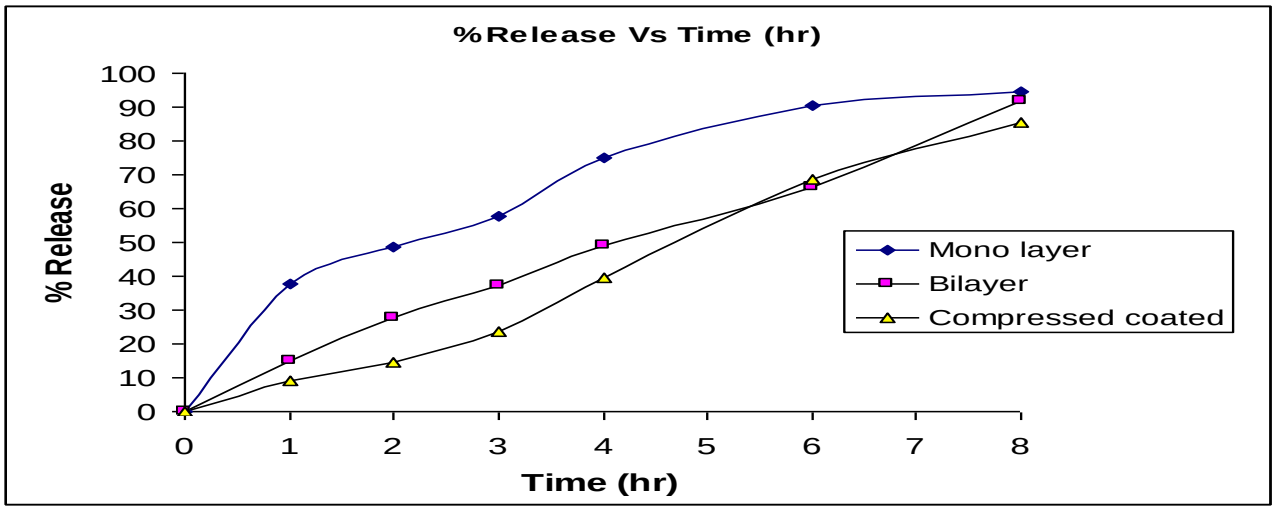

FIG. 12: CUMULATIVE DRUG RELEASE PROFILE OF MONOLAYER, BILAYERED AND COMPRESSED COATED TABLET

CONCLUSION: In the present work, the drug containing adhesive layer is matrix type tablet and prepared by wet granlulation technique, the backing layer was prepared by direct compression using Ethocel N10 and lake of sunset yellow. The prototype formulations of buccoadhesive bilayered tablet were prepared using increasing amount of HPMC K4M CR and Carbopol 974 P NF in 1:1 ratio to select the levels of these two polymers in factorial design. The prepared tablets of the prototype series were evaluated for Physical characters, Assay, Swelling index, Adhesion study and in-vitro drug release. Hence formulation containing HPMC K4M CR has shown the better results compared to innovator product.

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