ISSN: 2320 - 4230

Journal of Drug Discovery and Therapeutics

Available Online at www.jddt.in

CODEN: - JDDTBP (Source: - American Chemical Society)

Volume 6, Issue 2, February: 2018, 10-19

Research Article

FORMULATION AND CHARACTERIZATION OF CONTROLLED RELEASE BUCCOADHESIVE BILAYERED TABLET OF PROCHLORPERAZINE MALEATE

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ABSTRACT

Preformulation studies are the first step in the rational development of dosage form of a drug substance. The objective of pre formulation studies are to develop a portfolio of information about the drug substance, so that this information useful to develop formulation.API and excipients are to be thoroughly mixed in predetermined ratiofor compatibility studies,there is no color change and no lumps observed in sample charged at 40ºc/75%RH for 1 month and 60ºc for 15 days, A differential scanning calorimeter was used for thermal analysis of drug and mixture of drug and excipients, Five ml of sample was withdrawn from this solution and dilute up to 25 ml phosphate buffer pH 6.8 in 25 ml amber colored volumetric flask and absorbance of this solution was measured at 255 nm. in U.V. Buccoadhesive bilayered tablet of Prochlorperazine maleate were prepared by wet granulation technique using different concentration of Hydroxipropyl methylcellulose (HPMC K4M CR premium) and Carbomer (Carbopol 974 P NF) in equal ratio.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.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.All the Prepared bilayered tablets of the trial series were evaluated for following official and unofficial parameter like Physical characterization**,** Drug content**,** Swelling index**,** Bioadhesive strength**,** *In-vitro* drug release.

KEY WORDS: Tablet, Buccoadhesive, Prochlorperazine maleate, Carbopol 974 P NF

1. INTRODUCTION:

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].Since sublingual administration of drugs interferes with eating, drinking and talking, this route is generally considered unsuitable for prolonged administration. On the other hand, the duration of buccal drug administration can be prolonged with saliva activated adhesive polymers without the problems of sublingual administration[1, 2]Within the oral mucosal cavity, delivery of drugs can be classified into three categories:

- **Sublingual delivery**, which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth
- **Buccal delivery**, which is drug administration through the mucosal membranes lining the cheeks (buccal mucosa)
- **Local delivery**, which is drug delivery into the oral cavity.

2. EXPERIMENTAL WORK:

Table 2.1: Material used

Sr. No.	Material	Manufacture
1	Prochlorperazine maleate	Amol Drug Parma Ltd.
2	HPMC K4M CR	Colorcon
3	Carbopol 974 P NF	Noveon
4	Ethocel N10	Colorcon
5	Isopropyl alccohol	Samir tech. chem. Pvt. Ltd.
6	PVP K/30	Signet Chemicals Corporation
7	Sucrose	Alembic Limited
8	Talc	Lar Chem Industries
9	Magnesium stearate	Vasundhara Rasayans Ltd

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10	Lake of sunset yellow	Colorcon
11	Potassium dihydrogan ortho phosphate	Merck Limited
12	Sodium hydroxide	Qualigens Fine Chemicals
13	Sodium Chloride	Merck Limited
14	Pottasium Chloride	Merck Limited
15	Calcium Chloride	Merck Limited
16	Magnesium Sulfate	Merck Limited
17	Glucose	Alembic Limited
18	Sodium Bicarbonate	Merck Limited

Table 2.2: Equipments used

Sr. No.	Equipment /instrument	Make
1	Balance	Shimadzu
2	Halogen moisture balance	Mettler Toledo
3	Hot air oven	Polar Industries
4	Dehumidifier	Tropical Nortec
5	Magnetic stirrer with hot plate	Schott
6	pH meter	Lab india
7	Tray drier	Cintex
8	8 Station compression machine	Cadmach
9	Sieve shaker	Cisa
10	Water purifier	Barnstead
11	Peristaltic pump	Masterflux L/S
12	Magnetic stirrer with heating mantle	Cintex
13	Friability tester	Electrolab
14	Vernier calipers (digital)	Miyutoyo
15	Hardness tester 8M	Dr. Schleunger
16	Cleaning machine	Roots multiclean Ltd
17	Hygrometer	Shooze
18	Standard weight box	Mettler
19	Induction heat sealer	Cintex
20	Thermometer	Shoze
21	Dissolution test apparatus USP	Electrolab
22	Oscar ultrasonics	Oscar

2.1 PROFILE OF PROCHLORPERAZINE MALEATE[3-4].

Prochlorperazine maleate is a potent phenothiazine antipsychotic now largely used as an antiematic and to treat the vertigo.

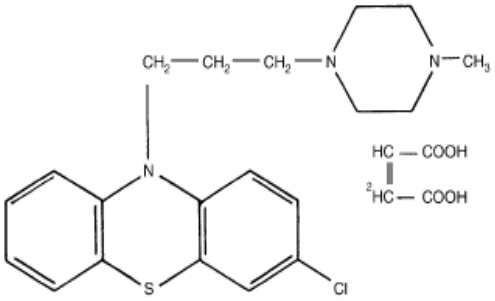

Fig. 2.1: Structure of Prochlorperazine maleate

CHEMISTRY

IUPAC Name: 2-Chloro-10-[-3-(-4-methyl-1-piperzinyl)-propyl] phenothiazine dihydrochloride

Molecular Weight: 606.1

Molecular Formula: $C_{20}H_{24}N_3SCl$, $C_4O_4H_4$

Description: White or pale yellow, Crystalline powder, practically odor less

Solubility: Very slightly soluble in water and in ethanol, practically insoluble in chloroform and ether.

PKa: 8.1

Half life: The plasma half life of the Prochlorperazine maleate is 6.7 to 6.8 hrs.

Volume of distribution: The volume of distribution of Prochlorperazine maleate is 23 liter/Kg

Clearance: Plasma clearance about 148 Liter/min

Protein binding: Prochlorperazine maleate shows the high protein binding (90 to 93 %)

Bioavailability: The bioavailability of Prochlorperazine maleate after oral administration is 0 to 16 %

Metabolism: Drug is mainly metabolized by sulfoxidation and hydroxylation followed by conjugation

Packing and storage: Store in well close light resistant container

3. FORMULATON OF BUCCOADHEIVE BILAYERED TABLETS OF PROCHLORPERAZINE MALEATE.

3.1 Preparation of drug containing adhesive layer.

Buccoadhesive bilayered tablet of Prochlorperazine maleate were prepared by wet granulation technique using different concentration of Hydroxipropyl

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.

3.2 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.

3.3 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.

Table 3.1: Composition of formulation of Trial series

Ingredients	F0	F1	F2	F3	F4	F5	F6	F7	F8
Drug Containing Adhesive Layer									
Prochlorperazine Maleate	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
Lack of sunset yellow	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4

All the quantities are in mg.

4. EVALUATION OF BUCCOADHESIVE BILAYERED TABLET

All the Prepared bilayered tablets of the trial series were evaluated for following official and unofficial parameter

- ❖ Physical characterization
- ❖ Drug content
- ❖ Swelling index
- ❖ Bioadhesive strength
- ❖ In-vitro drug release

4.1 Physical characterization

4.1.1 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%.

4.1.2. 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.

4.1.3. 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.

Table 4.2: Results of physical characterization of factorial series

Batch no	Weight (gm)		Hardness (Kp)		Thickness (mm)	
	Adhesive	Total	Adhesive	Total	Adhesive	Total
SA1	49.8 (±0.224)	90 (±0.2)	2.66 (±0.207)	5.98 (±0.239	0.916 (±0.011)	1.51 (±0.016)
SA2	49.58 (±0.683)	89.598 (±0.547)	2.69 (±0.114)	5.982 (±0.374)	0.968 (±0.016)	1.488 (±0.013)
SA3	49.06 (±0.590)	90.54 (±0.77)	2.66 (±0.182)	6.26 (±0.258)	0.872 (±0.019)	1.466 (±0.021)
SB1	49.88 (±0.712)	90.24 (±1.045)	2.718 (±0.144)	5.912 (±0.425)	0.988 (±0.052)	1.474 (±0.015)
SB2	50.1 (±0.552)	89.38 (±0.576)	3.06 (±0.114)	5.96 (±0.114)	0.91 (±0.018)	1.42 (±0.016)
SB3	49.8 (±1.187)	90.56 (±1.172)	2.692 (±0.166)	6.19 (±0.210)	0.962 (±0.041)	1.472 (±0.008)
SC1	50.06 (±1.069)	90.02 (±0.936)	2.702 (±0.142)	5.99 (±0.468)	0.966 (±0.046)	1.55 (±0.048)
SC2	49.88 (±0.856)	89.92 (±0.421)	2.678 (±0.081)	6.388 (±0.187)	0.984 (±0.009)	1.528 (±0.037)
SC3	49.94 (±0.207)	8.74 (±0.358)	2.88 (±0.148)	6.08 (±0.179)	0.986 (±0.015)	1.51 (±0.031)

Each reading is an average of three determinations (Avg.± S.D)

4.1.4 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.

Table 4.3: 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)

Each reading is an average of three determinations (Avg.± S.D)

Table 4.4: Results of the assay of trial series

Batch code	Drug content
F0	97.01
F1	97.98
F2	101.07
F3	98.59
F4	101.50
F5	99.78
F6	100.44
F7	101.67
F8	100.43

4.1.5. Swelling index: The water uptake of bilayered tablets in a phosphate buffer pH 6.8 was determined by gravimetrically. The backing layer side of the preweighed tablet was attached to preweighed glass cover slip using a cyanoacrylate adhesive. The support with the tablet was introduced in to a Petridis containing 15 ml of phosphate buffer pH 6.8. At a predetermined time interval, 0.5hr, 1hr, 1.5hr, 2hr, 3hr, 4hr, 5hr, and 6hr, the device were removed from the medium with the aid of a pair of forceps, and blotted with filter paper to remove the excess of water. Then the device immediately weighed and again introduce in to the same Petridis. The water uptake or swelling index of the bilayered tablet was calculated from the relative weight gain according to the following equation.

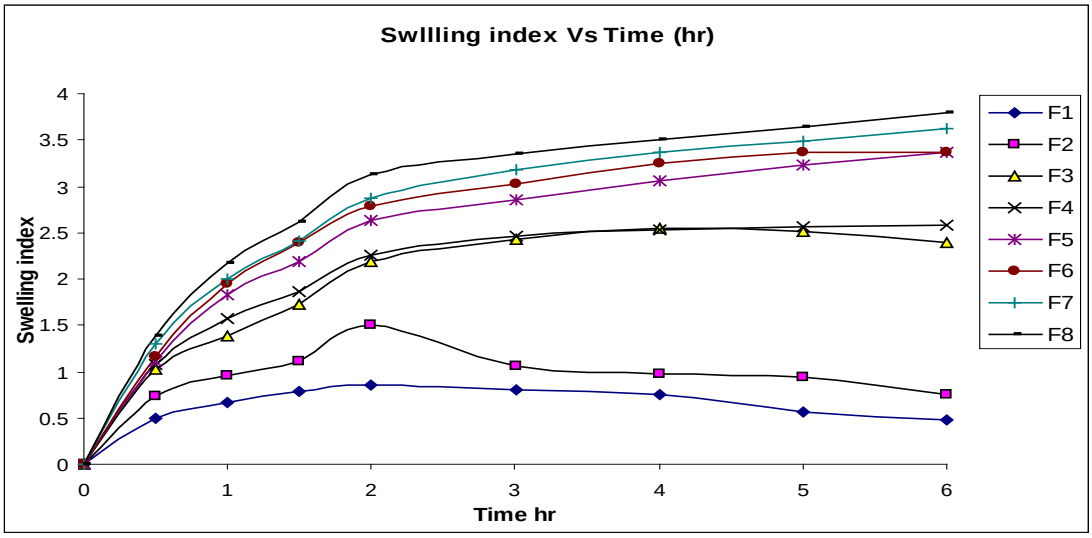

Fig.4.1: Graph of the Swelling index versus Time (hr) of trial series

Table 4.5: 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)

Each reading is an average of three determinations (Avg.± S.D)

4.2 *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 Electrolab 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 adhesive layer of the tablet was place to the bottom of the basket and when temperature achieved to 37±0.5ºc, dissolution apparatus was started. The protocol of the dissolution apparatus was sated for automatic 10ml sample withdrawal and replacement of fresh media at predetermined time interval i.e. 1hr, 2hr, 3hr, 4hr, 6hr,and 8hr. The dissolution apparatus was covered with the black col0ure polythine to protect the solution from light.The collected samples were filtered through the 0.45 um mdi filter and absorbance of the solution was measured at 255 nm. The concentration of Prochlorperazine maleate was calculated using slope of calibration curve and cumulative percentage release was calculated. The average and standard deviation of the three units was calculated and a graph of average percentage cumulative release versus time in hours was plotted.

Table 4.6: Percentage Cumulative drug release profile of batch no F_{HP}, F_{CP} and F2

Time (hr)	Cumulative percentage release of batch no.		
	F4	F_{HP}	F_{CP}
0	0.00	0.00	0.00
1	17.56(±0.815)	32.76(±1.981)	18.48(±0.616)
2	30.23(±1.86)	41.42(±0.737)	38.78(±1.078)
3	47.36(±0.18)	49.22(±1.087)	54.33(±1.76)
4	64.11(±1.18)	56.75(±0.643)	65.75(±1.149)
6	81.37(±0.896)	70.15(±1.443)	85.88(±0.309)
8	90.02(±2.317)	77.24(±1.421)	94.1(±0.526)

Each reading is an average of three determinations (Avg.± S.D)

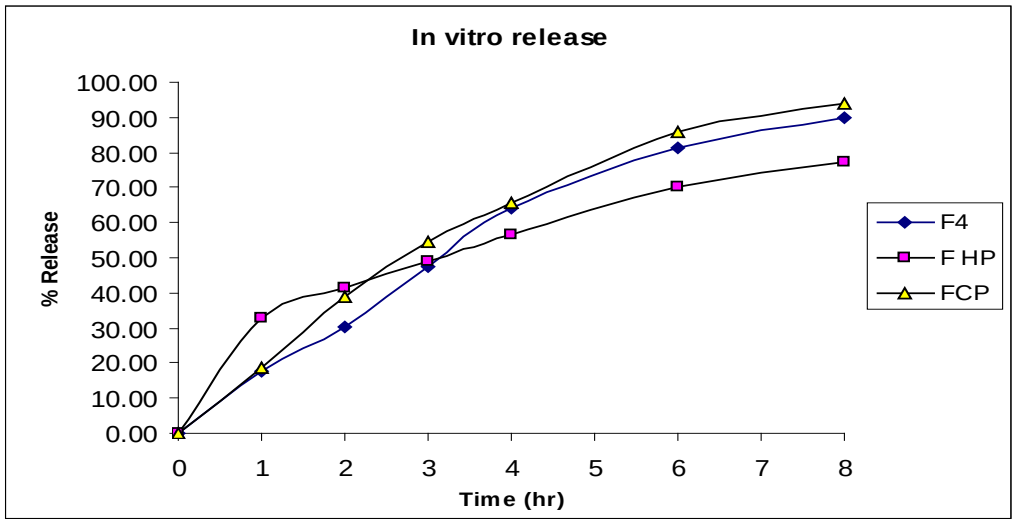

Fig.4.2: Plot of cumulative drug release versus time

5. FORMULATION OF FACTORIAL SERIES: On the basis of the results of the trial series a 3^2 full factorial design was constructed. In this factorial design the amount of the HPMC K4M CR and carbopol P974 NF was selected as the two factors and labeled as X_1 and X_2 respectively. The level of this factor is the amount of the HPMC and Carbopol, selected on the basis of the results of the trial series. 5%, 10% and 15% were selected as the level of the factor and denoted as Lower (-1), Middle (0) and Upper (1) level respectively. All other formulations and processing parameters were kept invariant throughout the study, except the amount of the sucrose that varied with the amount of the polymer. Table no.5.1 summarizes the experimental runs, their factor combination and table no34. Shows the translation of the coded levels to the experimental units used in study.

Table 5.1: A 3^2 full factorial experimental design lat out

Batch no		Experimental run	Coded factor level		Polymer combination	
			X1	X2	HPMC mg	Carbopol mg
SA	SA1	1	-1	-1	2.5	2.5
	SA2	2	-1	0	2.5	5
	SA3	3	-1	1	2.5	7.5
SB	SB1	4	0	-1	5	2.5
	SB2	5	0	0	5	5
	SB3	6	0	1	5	7.5
SC	SC1	7	1	-1	7.5	2.5
	SC2	8	1	0	7.5	5
	SC3	9	1	1	7.5	7.5

Table 5.2: Translation of coded level in actual unit

Coded Level	Unit	-1	0	1
X_1: HPMC K4M CR	mg	2.5	5	7.5
X_2: Carbopol 974 P NF	mg	2.5	5	7.5

5.1. Formulation of the Factorial series: The quantities of each ingredient in the formulation of the factorial series were shown in table no.5.3. The bilayered buccoadhesive tablets using this formulation were prepared by using same process followed for the trial series.

Table 5.3: Composition of formulation of factorial series

Ingredients	SA			SB			SC		
	SA1	SA2	SA3	SB1	SB2	SB3	SC1	SC2	SC3
Drug Containing Adhesive Layer									
Prochlorperazine Maleate	3	3	3	3	3	3	3	3	3
HPMC K4M CR	2.5	2.5	2.5	5	5	5	7.5	7.5	7.5
Carbpol974P NF	2.5	5	7.5	2.5	5	7.5	2.5	5	7.5
Sucrose	40	37.5	35	37.5	35	32.5	35	32.5	30
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
Lack of sunset yellow	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4

All the quantities are in mg

6. INTERPRETATION OF FACTORIAL DESIGN

Interpretation of factorial design for batch optimization was done in 6 steps

1. Preparation of table for sources of variation (Amount of HPMC K4M and Carbopol 974 P NF) and the response parameter (adhesive strength, % release)

2. Multiple regression analysis, Full model and reduced mathematical model

3. Contour plots

4. Selection of check point batch

5. Surface response curve

Step 1: Table no.47 shows the sources of variation (Amount of HPMC K4M and Carbopol 974 P NF) and the response parameter (adhesive strength and % release) of the buccoadhesive bilayered tablet.The sources of variation were generated from the interaction of two factors (Amount of HPMC K4M and Carbopol 974 P NF) and their three levels (-1, 0, and 1). The response parameter is adhesive strength in gm, and drug release at 4 hr.

Table 6.1: Sources of variation and response parameter

Run	Independent variables and it's interaction							Adhesive strength	% Release at 4 hr
	X1	X2	X1X2	$X1^2$	$X2^2$	$X1^2X2$	$X2^2X1$	Y1	Y2
1	-1	-1	1	1	1	-1	-1	8.935	20.77
2	-1	0	0	1	0	0	0	12.17	77.74
3	-1	1	-1	1	1	1	-1	22.23	76.45

4	0	-1	0	0	1	0	0	13.99	50.92
5	0	0	0	0	0	0	0	19.93	64.11
6	0	1	0	0	1	0	0	30.21	49.23
7	1	-1	-1	1	1	-1	1	15.47	55.87
8	1	0	0	1	0	0	0	29.36	47.00
9	1	1	1	1	1	1	1	40.12	37.00

7. SUMMARY AND CONCLUSION: Prochlorperazine maleate is an anti-emetic drug. It is under goes extensive first pass metabolism resulting in an oral bioavailability of 0 to 16 % and it shows variable absorption from GIT.Buccal route offers several advantages such as rapid absorption, high blood level and ease of administration and termination of therapy. 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 prolonged period of time.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. The levels of these two polymers were selected based on the results of the Swelling index, Adhesion study and in-vitro drug release.

Results of the study of individual polymers shows that the HPMC K4M CR alone was not able to controlled the release in first hour. Drug release from Carbopol 974 P NF alone was not approaching to zero order. Release of Prochlorperazine maleate from combination of HPMC K4M CR and Carbopol 974 P NF gave the good results compared to employing individual polymers.

On the basis of the results of the prototype series a 3^2 full factorial design was constructed. According to the factorial design the amount of the HPMC K4M CR and carbopol P974 NF was selected as the two factors. 5%, 10% and 15% were selected as the level of the factor and denoted as Lower (-1), Middle (0) and Upper (1) level respectively. All other formulations and processing parameters were kept invariant throughout the study, except the amount of the sucrose that varied with the amount of the polymer. The prepared buccoadhesive bilayered 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 SB3 containing 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 bioadhesive strength of this formulation was found to be 30.21gm and tablets of this formulation were able to adhere more than 8 hr. The drug release pattern of this formulation was found to be non-fickian and approaching zero order kinetics. The permeation flux was found to be 195.26 ug/sq.cm/hr. Reproducibility of the optimized formulation was checked and it was found that all the parameter were reproducible and found satisfactory. Stability study of the optimized formulation was carried out and there was not any significant change with respect to Adhesive strength, in vitro residence time, in vitro drug release and in vitro permeation study.

A mathematical model also was prepared by interpretation of 3^2 factorial design to predict the bioadhesive strength and % release at 4 hr and validated by ANOVA test. The results of bioadhesive strength and percentage release at 4hr obtained by contour plot were similar to that obtained by experiments.

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