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FORMULATION AND IN VITRO EVALUATION OF BUCCAL TABLETS OF CHLORPROMAZINE HCL.

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ABSTRACT

The aim of study was to prepare and characterize buccal tablets of Chlorpromazine HCl. using different Mucoadhesive polymers such as Sodium alginate, PVP K30 and HPMC K100M in combination. six formulations were prepared with varying concentrations of polymers using combination of two polymers in each formulation. Formulations F1 to F3 were composed of PVP K30 and HPMC K100M mixture in polymer mixture ratios of 1:2 to 2:1 where as formulations F4 to F6 were composed of PVP K30 and Sodium Alginate mixture in same polymers mixture ratios. The prepared tablets were evaluated for physicochemical parameters such as hardness, thickness uniformity, weight variation, surface pH, and moisture absorption studies. The prepared tablets were also evaluated for bioadhesive strength and in vitro drug release. In vitro bioadhesive strength and in vitro release studies showed that formulation F1 containing 1:2 ratio of polymers combination showed optimum bioadhesive and exhibited optimum drug release. The results indicate that the mucoadhesive buccal tablets of Chlorpromazine HCl. may be good choice to bypass the extensive hepatic first pass metabolism with an improvement in the bioavailability of Chlorpromazine HCl. through buccal mucosa.

KEYWORDS: Chlorpromazine HCl, buccal tablets, HPMC, control release, swelling index.

INTRODUCTION

Oral route is the most commonly employed route for a lot number of drugs administered. Some drugs which are susceptible to highly acidic condition of stomach and posses high first pass metabolism, this route fails to attend bioavailability. To overcome this problems various mucoadhesive systems are designed which are given by other than oral route like buccal, nasal, vaginal. Nowdays various newer researches are carried out on mucoadhesive drug

delivery systems. Various category of drugs like antihypertensives, antianginal, analgesics, anti-inflammatory, ophthalmic, hormonal in a which mucoadhesive system are formulated.[1]

Ideally buccal dosage form must maintain its position in the mouth for a few hours and for that strong adhesive contact to the mucosa should be established by using mucoadhesive polymers as excipients. Drug release should be in a controlled fashion and in a unidirectional way towards the mucosa. If the mucoadhesive excipients are able to control drug release, the drug release criteria can be fulfilled by preparing a system have uniform adhesiveness and impermeable backing layer. Various mucoadhesive devices such as include tablets, film, patches, discs, strips, ointments and gel have been recently developed.[2]

Limited studies, however, exist on novel devices that are superior to those of conventional buccal adhesive systems for the delivery of therapeutic agents through buccal mucosa.[3] Mucoadhesive polymers have been utilised in many different dosage forms in efforts to achieve systemic delivery of drugs through the different mucosa. These dosage forms include tablets, patches, tapes, films, semisolids and powders.[4]

Chlorpromazine HCl.is chemically 2-Chloro-10-(3-dimethylaminopropyl)phenothiazine hydrochloride blocks post-synaptic D_2 dopamine receptors. It is considered that dopamine receptor blockade in the mesolimbic area accounts for the antipsychotic effect, whilst blockade in the nigrostriatal system produces the extrapyramidal effects associated with chlorpromazine use. The anti-emetic effect results from dopamine antagonism in the chemoreceptor trigger zone. Chlorpromazine also possesses antimuscarinic properties. It is an antagonist at histamine (H_1), serotonin and alpha-1-adrenergic receptors.[5]

MATERIAL AND METHOD

Materials

Chlorpromazine HCl. was received as gift sample from Analytical Solutions Ltd**.,** Navi Mumbai, Maharashtra. PVP K30 and Hydroxy Propyl Methyl cellulose (HPMC) were also received as gift sample from Analytical Solutions Ltd., Navi Mumbai. Sodium alginate procured from Loba chemie Ltd. All other reagents and chemical used of analytical grade.

Method

Chlorpromazine HCl. was mixed manually in polybags with different ratios of PVP K30 and HPMC K100M mixture or PVP K30 and Sodium alginate mixture as mucoadhesive polymers

and mannitol as diluent (table 1) for 10 mins. The blend was lubricated with magnesium stearate for 3-5mins and talc was added as glidant. Then mixed blend was compressed into tablets by direct compression method using 8 mm flat punches in a Minipress I Rimek tablet punching machine. Each tablet (175 mg) contains 25 mg of Chlorpromazine HCl.

Evaluation of Tablets

Weight variation[6]

The weight of tablet is measured to ensure that the tablet conatins proper amount of drug .20 tablets were taken at random for the test and were weighed individually and the average weight was also calculated. Table 11 gives the specifications for the tablet deviation allowed as per Indian Pharmacopoeia.

Hardness

The crushing strength (kg/cm^2) of tablets was determined by using Monsanto hardness tester. The pressure required to break the tablet diametrically was measured.

Thickness and Diameter

Thickness and diameter in mm of tablets was determined by using Vernier Calliper.

Friability[6]

In this test 20 tablets were weghed and placed in a Roche friabilator test apparatus, the friabilator was operated at 25 rpm for 100 revolutions. After 100 revolutions the tablets were removed, de-dusted and weighed again. The friability was determined as the percentage loss in weight of tablets.

$$\% \text{ Friability} = \mathbf{1} - \frac{\text{weight of tablets after test}}{\text{Weight of tablets before test}} \times 100$$

Drug content[7,8]

Powder one tablet, shake 1 ml of dilute Hcl and 401 ml of water for 15 min, and add sufficient water to produce 100 ml and mix. Centrifuge about 15 ml and to 10 ml of the clear, supernatant liquid add 2 ml of 1M Hcl and sufficient water to produce a solution containing about 0.005 % w/w concentrated. Hcl .Measure the absorbance of the resulting solution at the max. at about 254 nm. Calculate the content of C17H19Cl N2S. HCl in the tablet. According to BP limits for tablet of Chlorpromazine HCl. Contains not less than 92.5 percent and not more than 107.5 percent Chlorpromazine HCl.

Disintegration Time[9]

Disintegration test on tablets was carried out. Six tablets from each batch were put into each tube of the disintegration basket maintained in distilled water at 37.5˚C as a media of disintegration. The British Pharmacopoeial specification for maximum disintegration time for coated and uncoated were used to evaluate the samples. Tablets were completely disintegrated when all the particles pass through the mesh.

Surface pH study[10]

The surface pH of buccal tablets is determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may cause irritation of buccal mucosa, so we tried to keep the pH as close to neutral as possible. For this purpose a combined glass electrode is used. The tablet is allowed to swell by keeping it in contact with 10 ml of phosphate buffer pH 6.8 in petri plate for 2 hrs at room temperature. The pH is recorded by bringing the electrode on the tablet surface and allows equilibrating for 1 minute.

Swelling Index[11]

The swelling rate of buccal tablet is evaluated by using phosphate buffer pH 6.8.The initial weight of tablet is determined (w_1).The tablet is placed in pH 6.8 phosphate buffer (10 ml)in a petri dish at 37±1˚C and tablet is removed at different time intervals (01,02,04,06,08 and 10 hrs),then blotted with filter paper and reweighed (W2).the swelling index is calculated by the formula;

$$\text{Swelling Index} = 100 \times \frac{(W2 - W1)}{W1}$$

Matrix Erosion[12]

After swelling study, the swollen tablets were dried at 60˚C for 24 hr in an oven and kept in desccicator for 48 hrs and reweighed again (W3) .The Matrix erosion was calculated by using the formula given below;

$$\% \text{ Matrix Erosion} = 100 \times \frac{(W_1 - W_3)}{W_3}$$

Mucoadhesion strength[13,14]

The apparatus used for bioadhesion testing was assembled in laboratory. Mucoadhesion strength of tablet was measured on a modified physical balance using the method described by Gupta et al using goat cheek pouch as model mucosal membrane.

A double beam physical balance was taken, the left pan was removed. A thick thread of suitable length was hanged to left arm. To the bottom side of thread a glass stopper with uniform surface was tied. A clean 500ml glass beaker was placed below hanging glass stopper and another glass beaker of 50 ml was placed in inverted position and weighed 50 gm to prevent floating. The balance was so adjusted that right hand side was exactly 5 gm heavier than left.

Method

The balance adjusted as described above was used for the study. The goat mucosal membrane excised and washed was tied tightly using thread over the base of inverted 50 ml glass beaker. The suitably weighed was lowered into 500ml beaker, which was then filled with isotonic phosphate buffer pH 6.8 kept at 37˚C such that the buffer reaches the surface of mucosal membrane keep it moist. This was then kept below left hand side of balance. The buccal tablet was then stuck to the glass stopper through its backing membrane using an adhesive(feviquick). The 5 gm on right hand side is removed; this causes application of 5 gm of pressure on buccal tablet overlying buccal mucosa. The balance was kept in this position for 3 minutes and then slowly weights were increased on the right pan, till tablet separate from mucosal membrane. The total weight on right pan minus 5 gm gives the force required to separate tablet rom mucosa. This gives bioadhesive strength in grams. Then mean value of 3 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 minutes before reading a new tablet of same formulation to get reproducible multiple results for the formulation.

Dissolution Study[15,16]

For any formulation drug release from the dosage form is the important parameter to be measured. Drug release of mucoadhesive buccal tablet of Chlorpromazine HCl.is evaluated by the dissolution test apparatus. The test was performed using USP type –II apparatus (Lab India Disso 2000) at 50 rpm and 900 ml of phosphate buffer pH 6.8 as dissolution medium. The temperature is maintained at 37±0.5˚C.One of the layers of buccal tablet is attached to glass slide with Cynoacrylate adhesive. The slide is placed at the bottom of the dissolution

vessel. Aliquots of 5 ml were withdrawn at predetermined time intervals of 1,2,4,6,8,10 Min. and the volume was replaced with fresh dissolution medium. Above 5 ml samples were filtered through whatmann filter paper and analysed for Chlorpromazine HCl. After appropriate dilution by measuring the absorbance at 254 nm.

Data of in vitro release was fitted into different equations to explain the release kinetics and release mechanism of Chlorpromazine HCl. from buccal tablets.

The kinetic equations used were zero order, first order and drug release mechanism models used were Higuchi, Korsmeyer-Peppas.

RESULT AND DISCUSSION

FTIR studies of chlorpromazine HCl

The IR spectrum of sample was recorded and the functional groups of Chlorpromazine HCl. Were found to be match with standard IR spectrum of Chlorpromazine HCl.

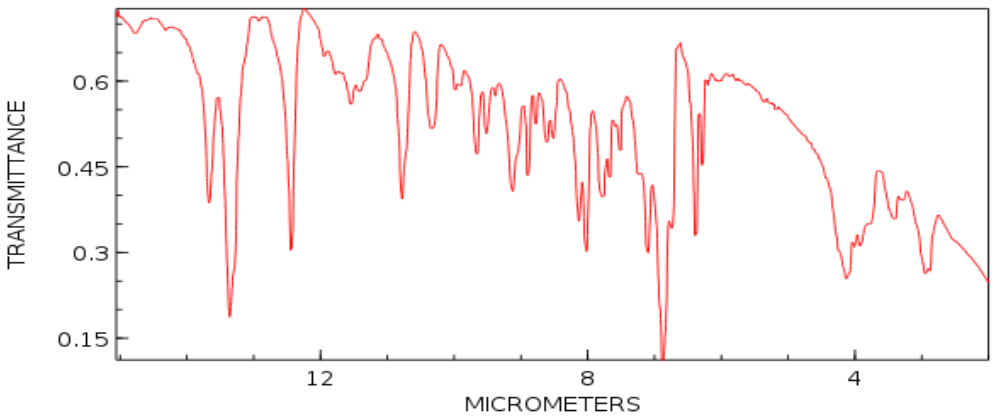

Fig. 1: FTIR spectrum of chlorpromazine HCl.

DSC Studies of Chlorpromazine HCl.

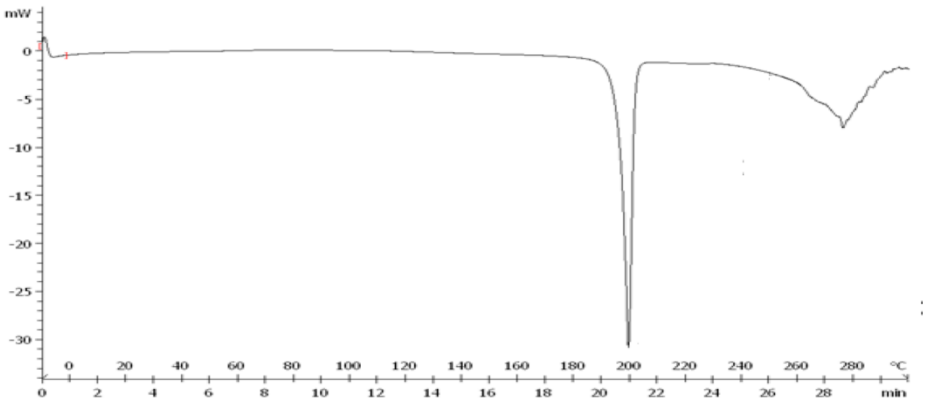

Fig. 2: DSC thermogram of Chlorpromazine HCl.

Drug Excipients compatibility study

Drug – excipients interaction study was carried out by using Fourier transform infrared spectroscopy(FTIR). FTIR spectra of Drug, physical mixture of Drug: Drug: PVP K30, Drug:HPMC K100, Drug:Sodium alginate are shown in following figures.

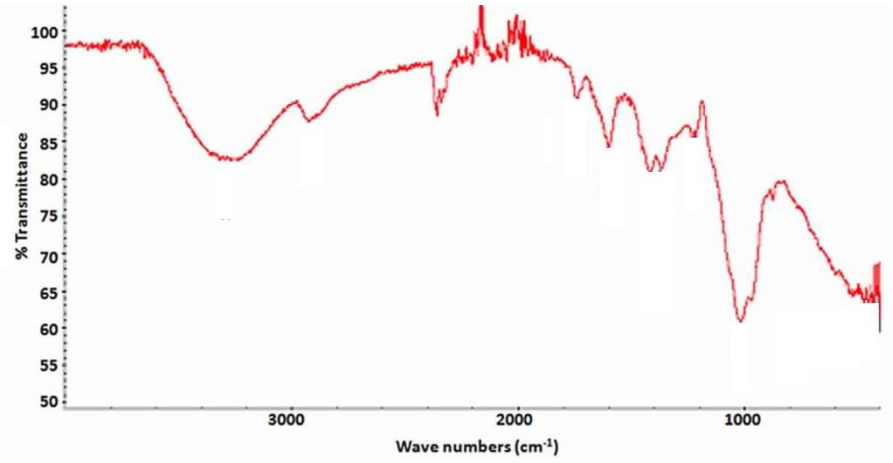

Fig. 3: FTIR spectra of Chlorpromazine HCl. and PVP K 30.

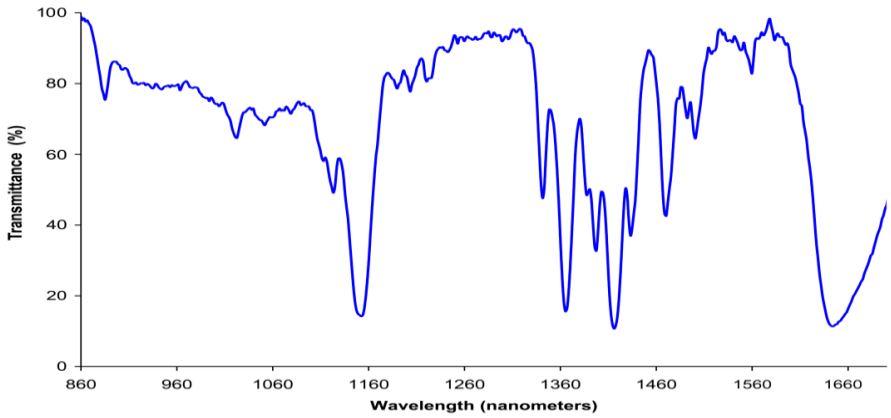

Fig. 4: FTIR spectra of Chlorpromazine Hcl. and HPMC K 100.

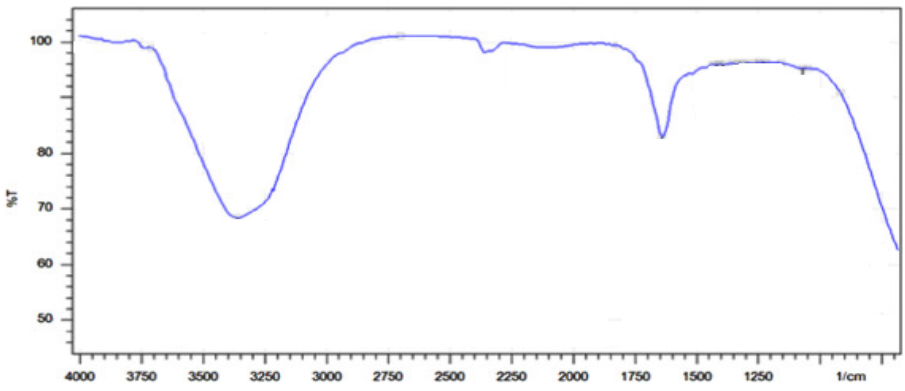

Fig. 5: FTIR spectra of Chlorpromazine Hcl. And sodium alginate.

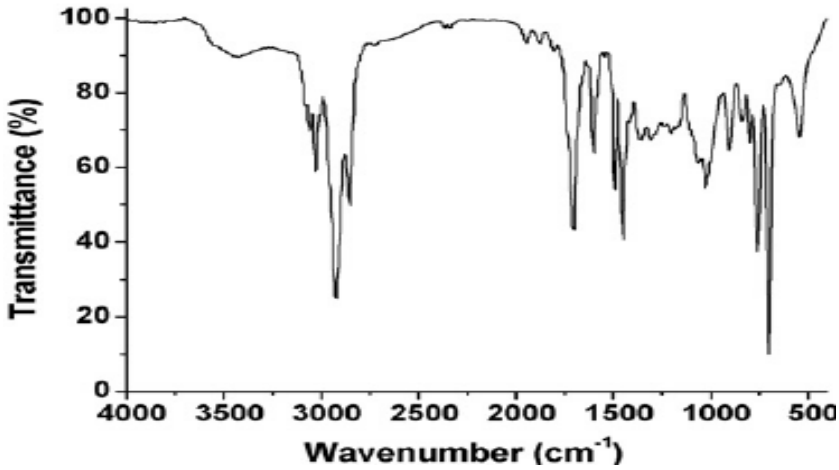

Fig. 6: FTIR spectra of Optimized batch F1.

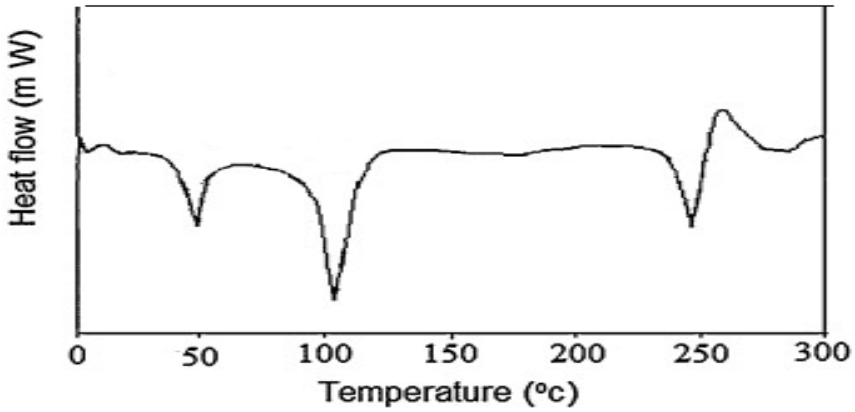

Fig. 7: DSC Thermogram of Optimized batch F1.

Table 1: Pre compression Evaluation of Powder mixture.

Formulation	Bulk Density (gm/cm^3)	Tapped Density (gm/cm3)	Carr's Index %	Angle of repose (θ)
F1	0.5887	0.6387	7.84	27.08
F2	0.5670	0.635	9.44	28.80
F3	0.5769	0.635	7.69	30
F4	0.5825	0.6593	11.65	23.67
F5	0.5885	0.6385	7.83	26.90
F6	0.5660	0.6060	6.6	31.52

Table 2: Post compression Evaluation of Tablets.

For mula code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)	Disintigration Time. (sec)	Surface pH
F1	175.1±0.83	3.99±0.01	5.56±0.12	0.77±0.02	99.97±0.008	31±1.15	6.89±0.01
F2	175.1±0.85	3.84±0.03	5.57±0.12	0.52±0.02	99.56±0.05	35±1.10	6.81±0-01
F3	175±0.93	3.65±0.01	5.50±0.13	0.85±0.01	99.36±0.09	35±2.35	6.65±0.04
F4	175±0.90	3.81±0.11	5.54±0.21	0.57±0.01	99.87±0.07	40±1.05	6.19±0.01
F5	174.9±0.65	3.85±0.13	5.67±0.16	0.75±0.01	99.23±0.8	44±2.01	6.63±0.09
F6	174.8±0.77	3.77±0.12	5.43±0.20	0.62±0.02	100.05±0.04	51±1.18	6.87±0.09

Table 3: Swelling index values of mucoadhesive buccal tablet of Chlorpromazine HCl.

Formula code	Time in hrs					
	1	**2**	**4**	**6**	**8**	**10**
F1	49.2	59.9	73.6	88.5	91.7	99.8
F2	49.5	60.1	71.9	88.6	93.3	96.6
F3	49.6	60.2	71.8	88.8	93.8	98.9
F4	45.3	54.9	65.1	83.6	87.1	90.1
F5	48.6	56.9	70.7	88.0	89.2	94.8
F6	49.5	60.1	71.9	88.6	93.3	96.6

Table 4: Matrix erosion of Mucoadhesive Buccal tablet of Chlorpromazine HCl.

Formula code	% Matrix Erosion
F1	9.30
F2	9.89
F3	9.51
F4	11.9
F5	10.3
F6	9.9

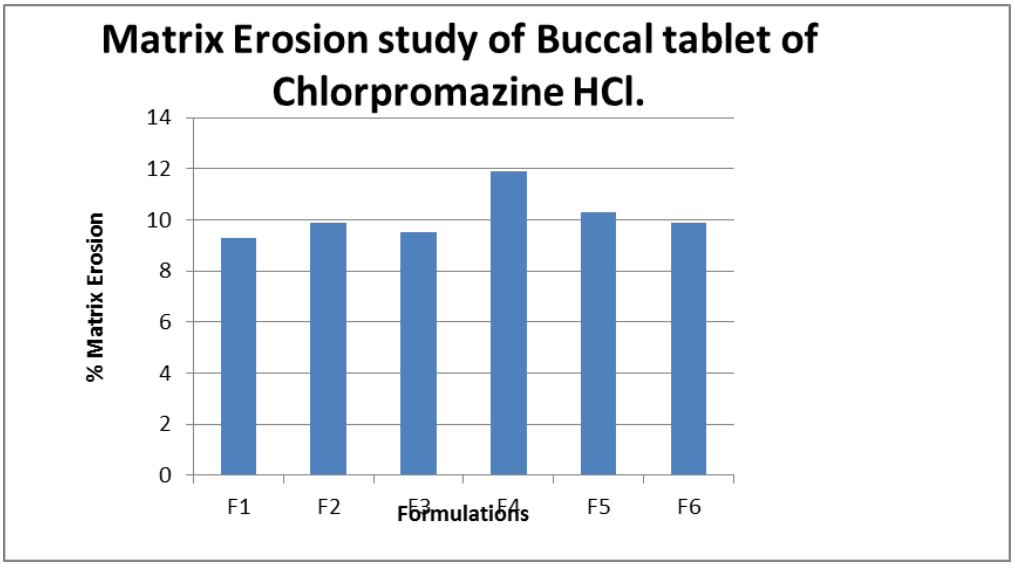

Fig. 8: Matrix Erosion Study of Buccal tablet of Chlorpromazine HCl.

Table 5: Mucoadhesive strength of buccal tablet.

Formula code	Mucoadhesive strength(gm)
F1	20.4
F2	19.24
F3	18.1
F4	17.40
F5	18.75
F6	19.38

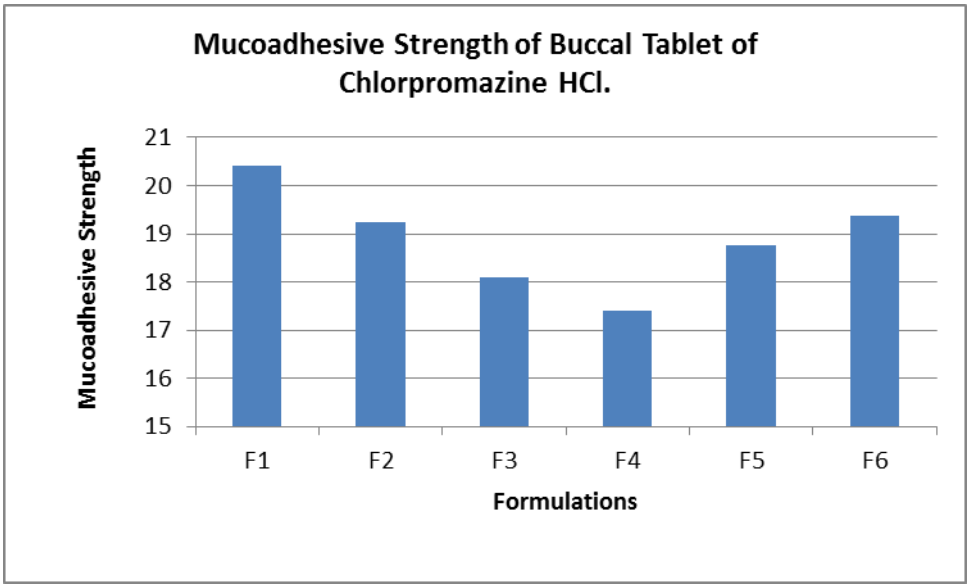

Fig. 9: Mucoadhesive strength of buccal tablet of Chlorpromazine HCl.

In vitro dissolution study: Release of drug from the buccal mucoadhesive tablet varied according to the type and ratio of matrix forming polymer. HPMC K 100 has excellent mucoadhesive, gelling properties and also helps in extending effect.

Table 6: % Cumulative drug release of Chlorpromazine HCl.

Time	F1	F2	F3	F4	F5	F6
1	12.01	11	10.76	9.62	8.08	6.93
2	20.52	18.17	16.65	14.37	12.1	10.76
3	29.18	26.81	25.28	20.61	18.27	15.93
4	38.68	37.48	34.36	29.27	25.75	23.03
5	50.24	46.30	42.41	36.12	33.72	31.75
6	62.27	58.31	54.36	50.33	42.52	38.55
7	74.40	70.51	66.41	59.27	57.97	55.87
8	78.98	74.95	70.92	66.78	65.83	63.34
9	87.45	83.35	79.68	78.57	73.89	70.87
10	98.70	95.69	91.58	87.42	84.71	81.17

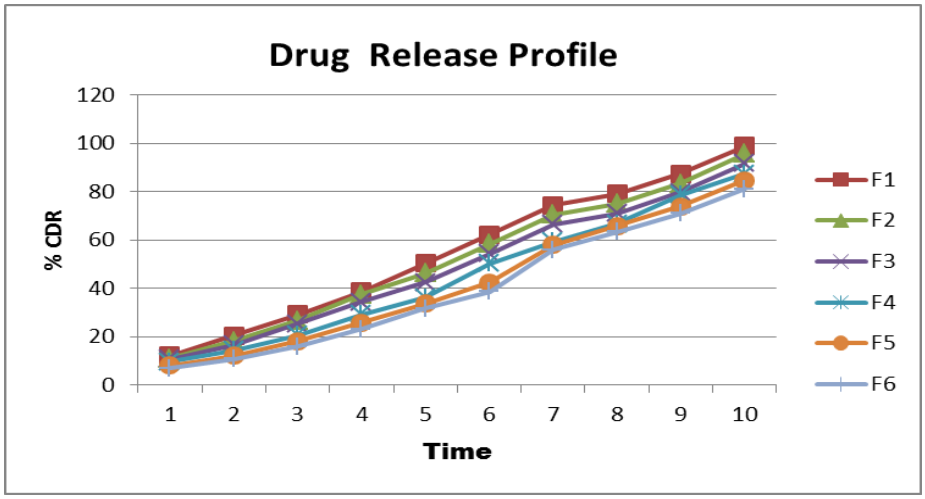

Fig. 10: Drug release profile of Chlorpromazine HCl.

Stability studies[17]

Stability studies were carried out on the tablets of batch F1 and F3 were first wrapped in aluminium foil then placed in an amber colored bottle. It stored at 40˚C for 45 days. Tablet was evaluated for physical characteristics; mucoadhesive properties, in vitro drug release and mucoadhesive strength study after 45 days. Results obtained were compared with data obtained for zero time at ambient temperature.

Table 7: Stability studies of Formulation F1 and F3.

Formula code	% drug release data						Drug content	Mucoadhesive strength on 45th day
	1st day	9th day	18th day	27th day	36th day	45th day		
F1	99.7	99.75	99.73	99.71	99.7	99.7	99.99	18.15
F3	91.6	91.2	91.49	91.42	91.4	91.4	99.24	21.2

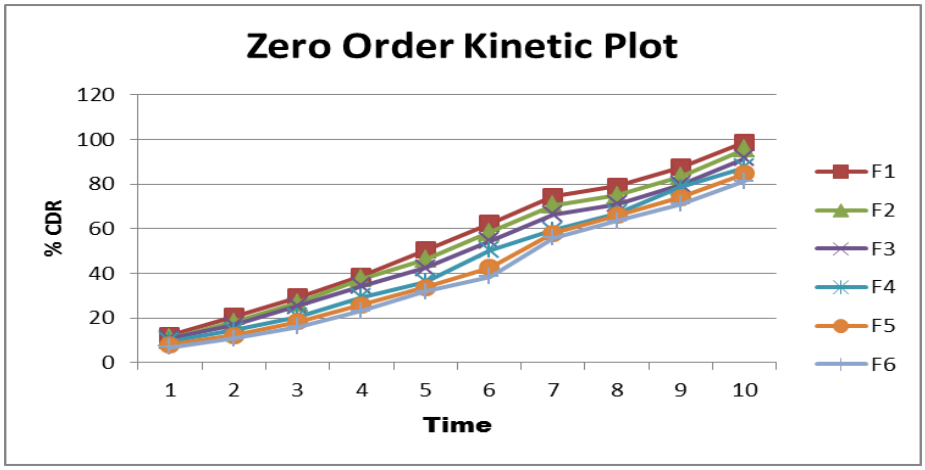

Fig. 11: Zero Order Kinetic Plot.

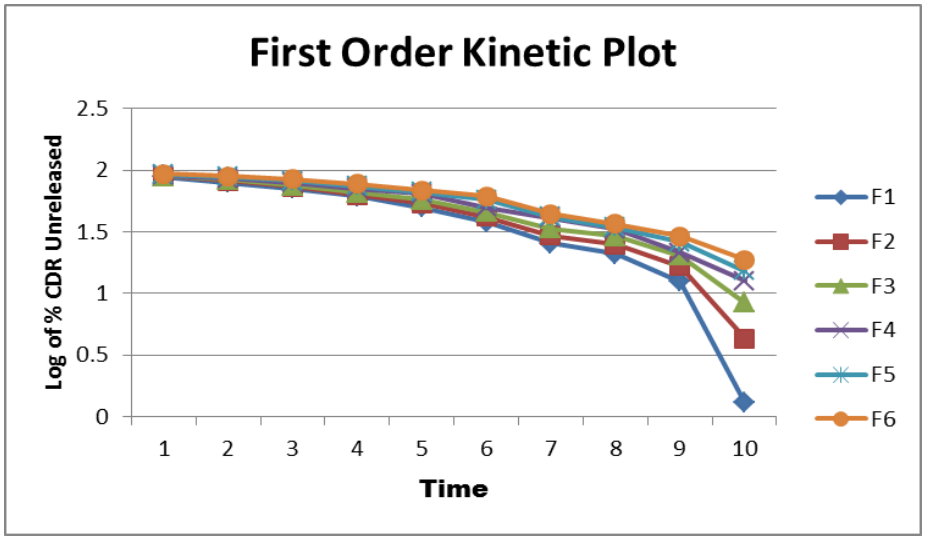

Fig. 12: First Order Kinetic Plot.

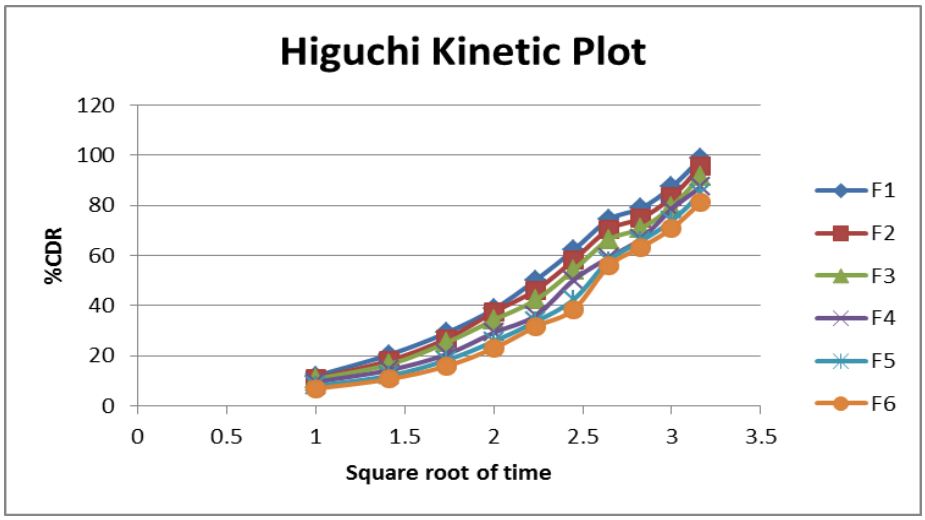

Fig. 13: Higuchi Kinetic Plot.

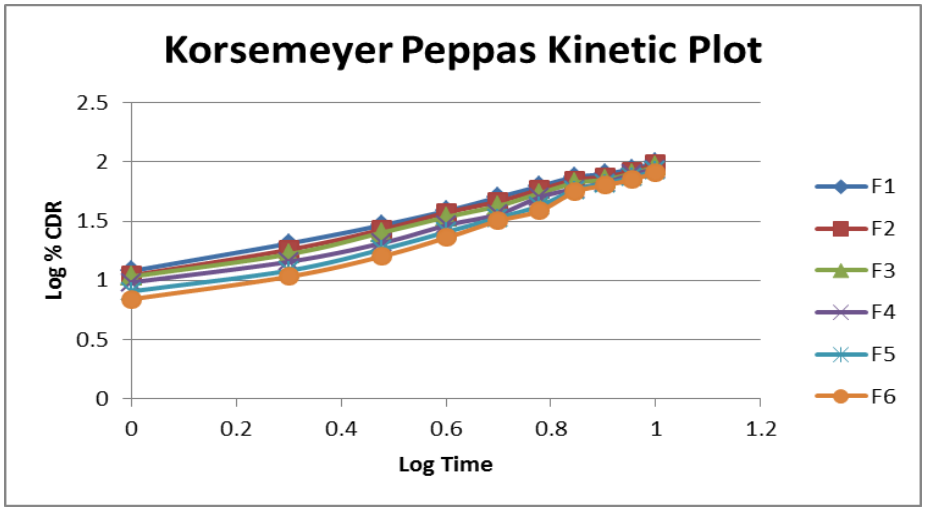

Fig. 14: Korsemeyer Peppas Kinetic Plot.

Kinetic treatment to dissolution data

Kinetic studies i.e. zero-order, first order and Higuchi and Korsemeyer Peppas were conducted for all formulations and the data is shown in Table 6. The value of regression correlation co-efficient (R^2) was evaluated for all the formulations which value was close to 0.99. Hence it is conducted that all the formulations are following the zero-order drug release

Table 8: Regression coefficients.

Formulations	Zero order	First order	Higuchi	Korsemeyer Peppas
F1	0.995	0.751	0.975	0.994
F2	0.995	0.836	0.972	0.993
F3	0.995	0.884	0.965	0.989
F4	0.990	0.901	0.945	0.978
F5	0.985	0.905	0.934	0.976
F6	0.980	0.914	0.926	0.974

Release rate constant

The release rate constant (k) of mathematical models for in vitro drug release of all formulations given below in table 9

Release rate constant(k) = Slope*2.303

Table 9: Release rate constants.

Formulations	Zero order	First Order	Higuchi Equation	Korsmeyer-Peppas
F1	22.56	-0.36	95.45	2.16
F2	21.91	-0.278	92.53	2.23
F3	21.00	-0.230	88.36	2.22
F4	20.72	-0.202	86.50	2.33
F5	20.45	-0.186	85.09	2.48
F6	19.97	-0.170	82.97	2.61

Drug release Mechanism

For all formulations Korsmeyer Peppas exponent (n) was found to be greater than 0.5 (>0.5).This indicated that mechanism of drug release controlled from the Chlorpromazine HCl. buccal tablet was based on diffusion phenomenon. The in vitro release kinetics exhibited a non fickian transport model. This kind of diffusion corresponds to a more predictable type of swelling-controlled system.

CONCLUSION

From the findings obtained in the research work, it can be concluded that.

FTIR and DSC studies revealed that there are no chemical interactions between Chlorpromazine HCl. and Polymers used in the study. The flow properties of polymer and drug were determined and found satisfactory. The tablets prepared were found to be good without any formulation defect as chipping, capping and sticking. The formulated tablets give satisfactory results for various physicochemical evaluations of tablets like dimensions, hardness, weight variation, friability, *in vitro* dissolution, mucoadhesive strength Surface pH, swelling index, matrix erosion and drug content. The low values of standard deviation for average weight and drug content of the prepared tablets indicate weight and drug content uniformity within the batches prepared. Based on mean dissolution time, formulation F1 was found to be promising. The overall study indicates that among the six Formulations F1 showed satisfactory mucoadhesive property, significant swelling property and optimum release profile. Hence it can be concluded that the formulation F1 will be useful for buccal administration. So, the mucoadhesive buccal tablets of Chlorpromazine HCl. are good choice to bypass the extensive hepatic first pass metabolism with an improvement in the bioavailability of Chlorpromazine HCl. Through buccal mucosa, at the same time reducing GI disturbances and improving patient compliance.

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