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OPTIMIZATION AND EVALUATION OF METOCLOPRAMIDE HCl AS MUCOADHESIVE BUCCAL PATCH

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ABSTRACT

Buccal drug delivery appeared as an innovative substitute to other conventional types of drug delivery systems. Within the oral mucosal cavity, the buccal region has rich blood supply and relative permeability that offers an attractive route for drug administration into the systemic circulation. This study involved formulation of metoclopramide HCl as bilayer mucoadheive buccal patch composed of medicated layer and backing layer to prevent undesirable drug release by utilizing solvent casting technique. The medicated layer was prepared by using hydroxyl propyl methyl cellulose as primary polymer and different secondary polymers including poly vinyl pyrolidone, Carpabol and sodium carboxy methyl cellulose in order to optimize the final formula. The backing layer was prepared by using ethyl cellulose and dibutyl phthalate as plasticizer. The results revealed that formula F4 containing hydroxyl propyl methyl cellulose (75mg) as primary polymer and poly vinyl pyrolidone (18.75 mg) as secondary polymer, propylene glycol as plasticizer (30% of total polymer weight), sodium saccharine as sweetening agent (4 mg) was chosen as selected formula in accordance to the surface pH (6.82), tensile strength (15.34), percentage elongation at break (26.75), swelling index (18.64), mucoadhesive strength (19.23gm), percentage moisture absorption (5.35), percentage moisture loss (4.81) and *Ex-Vivo* residence time (6.23hrs) which is satisfactory to give *invitro* release (92.34%) of metoclopramide HCl after 6 hrs. The research showed *invivo* drug release of 69.54% for selected formula, with *invitro- invivo* correlation equal to (0.9822) suggesting successful formulation that can be used mainly for patients having difficulties in swallowing, patients with nausea or vomiting, patients with upper gastrointestinal disease or surgery. Furthermore, to reduce first pass effect

with possible reduction in overall dosing, dose dependent side effect and frequency of administration.

KEYWORDS: Metoclopramide HCl, antiemetic, transmucosal, mucoadhesion, buccal patch.

INTRODUCTION

The buccal cavity in addition to by passing the first pass effect it consider as useful substitute to oral route for drug absorption in situations where the gastrointestinal route is unfeasible. These situations include patients with nausea or vomiting, patients with swallowing difficulties, in unconscious or incapacitated patients, drugs that cause gastric irritation.[1],[2] The buccal mucosa has constituency of smooth muscle and relatively fixed mucosa which makes it more desirable region for retentive systems used for oral transmucosal drug delivery. Consequently the buccal mucosa is more fitted for sustained delivery applications.[3] Over past few decades, the concept of use of bioadhesive polymers to elongate the contact time gained notable attention in transmucosal drug delivery.[4] The term 'mucoadhesion' can be defined as a process by which natural or synthetic polymer can stick to mucosal layer of biological membrane. The concept of mucoadhesive has reintroduced many researchers to the possibility that these polymers can be used to overcome physiological barrier in extended time drug delivery.[5]

Metoclopramide HCl is a substituted benzamide used for its prokinetic and antiemetic properties. Metoclopramide HCl is indicated for disorders of decreased gastrointestinal motility such as gastroparesis, gastroesophageal reflux disease, dyspepsia and in nausea and vomiting associated with various gastrointestinal disorders, with migraine, after surgery, with cancer therapy and to stimulate gastric emptying during radiographic examinations. Metoclopramide is rapidly and almost completely absorbed from GIT after oral doses, although conditions such as vomiting or impaired gastric motility may reduce absorption,[6] Up to about 60 of an oral dose undergoes first-pass metabolism but there is a considerable intersubject variation and this result in a wide range of oral bioavailability (60-90%).[7],[8] The half-life is about 4-6 hours, log p 2.6, pKa 9.3.[9] Hence, metoclopramide HCl is a suitable candidate for controlled buccal drug delivery. In the present investigation, optimization of prolong release bilayer buccal mucoadhesive patch for metoclopramide HCl is applied through studying different variables in an attempt to diminish the first pass effect with possible reduction in the overall dosing of the drug, dose dependent side effects, frequency of

administration, furthermore to be used for patients with nausea or vomiting, patients with upper gastrointestinal disease or surgery or those patients having difficulty in swallowing.

MATERIALS AND METHODS

Chemicals

Metoclopramide HCl (MCP HCl) was purchased from Provizer Pharma, India. Carpabol 940 and polyvinyl pyrolidine (PVP_{30}), were purchased from Alladin Industrial Corporation, Shanghai, China. Sodium carboxy methyl cellulose (Na CMC) was purchased from SDI, Iraq. Hydroxyl propyl methyl cellulose K4M (HPMC K4M) and Ethyl cellulose were purchased from Provizer Pharma, India. Propylene glycol (PG) was purchased from Panreac AAG, Spain. Dibutylphthalate was purchased from Fluka Chemika, Switzerland. Glycerin was purchased from GCC, UK. Sodium saccharine (Na saccharine) was purchased from Avonchem limited, UK. Poly ethylene glycol 400 (PEG 400) was purchased from Sinopharm Chemical Reagent Co, Ltd. China. All other reagents and chemicals used were of analytical grade.

Formulation of Bilayer Mucoadheive Buccal Patch

The bilayer mucoadheive patch was prepared by utilizing solvent casting technique method.[10] the mucoadheive layer was prepared by using HPMC K4M as primary polymer alone or in combination with secondary polymers $PVPK_{30,}$ Carpabol 940 and Na CMC in different ratios of total polymer weight 1500 mg as shown in table (1), all formulas were dissolved in 50 ml of distilled water, HPMC K4M was first dispersed in 20-30% of the required volume of 80-90 °C heated distilled water, after that sufficient amount of cold water was added to complete the volume with continuous stirring on magnetic stirrer[11], the secondary polymers were added after solubilization in sufficient amount of water with continues mixing, to all formulas sodium saccharine (sweetening agent) dissolved in distilled water and the calculated amount of MCP HCl such that each patch will have 10.5 mg of MCP HCl which is equivalent to 10 mg of MCP as a base, MCP HCl was added after levigation with 30 % of total polymer weight PG (plasticizer and permeation enhancer) while for formulas F5 and F6 glycerin and PEG 400 were added respectively instead of PG, the final mixture mixed continuously for 24 hrs and set aside until the mixture got free from bubbles. Then it was poured into previously prepared ethyl cellulose backing layer and left it to dry at 40 °C by hot air oven. The ethyl cellulose backing layer solution composed of ethyl cellulose 500 mg dissolved in 10 ml acetone and 0.2 ml of dibutyl phthalate, the solution was poured

into 9cm petridish on a leveled surface and then covered by inverted funnel to allow controlled evaporation at room temperature.[12] The dried patches carefully detached, checked for any inadequacies or air bubbles and cut into squares of 2 × 2cm^2 size, the patches were packed in aluminum foil and stored in a desiccator to conserve the integrity and elasticity of the patch until further use in patch evaluations.[13]

Table 1:- Composition of formulated MCP HCl mucoadhesive buccal patch

ingredients mg	Composition of medicated mucoadhesive layer of each patch											
	Formula code											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
MCP HCl	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5
HPMC	93.75	62.5	70.31	75	75	75	62.5	70.31	75	62.5	70.31	75
PVP		31.25	23.44	18.75	18.75	18.75						
Carpabol							31.25	23.44	18.75			
Na CMC										31.25	23.44	18.75
Na saccharin	4	4	4	4	4	4	4	4	4	4	4	4
PG	28.125	28.125	28.125	28.125			28.125	28.125	28.125	28.125	28.125	28.125
Glycerin					28.125							
PEG 400						28.125						

Composition of backing layer for each patch	
Ethyl cellulose	31.25 mg
Dibutyl phthalate	0.0125 ml

Physical Evaluation

A-Uniformity of Weight

The individual weights of three different randomly selected patches from each batch were weighed individually using digital balance and the average weight was calculated.[14]

B-Thickness

The thickness of three randomly selected buccal patches from every batch was determined at five different points in the center and four corners using digital vernier caliper.[15]

C-Folding Endurance

Folding endurance of the patch was determined by continually folding one patch at the same place till it broke or folded up to 300 times manually, which was considered satisfactory to reveal good patch properties. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance. This test was done on randomly selected three patches from each formula.[15]

D-Surface pH

The surface pH of the buccal patches was measured in order to examine the likelihood of any side effects *invivo*. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to maintain the surface pH nearby to neutral as possible. A combined glass electrode was used for measuring the surface pH. The patch was allowed to hydrate by keeping it in contact with 1 ml of distilled water for 1 hour at room temperature. The pH was measured by bringing the electrode in contact with the surface of the patch and allowing it to equilibrate for 1 minute and the results were checked by using litmus paper. The experiments were performed in triplicate, and average values were reported.[15]

Content Uniformity

The patch was allowed to dissolve in 100 mL phosphate buffer pH 6.8 contained in a beaker, and placed on temperature controlled magnetic stirrer maintained at 37 $^{\circ}$C. The medium was stirred at 300 rpm with magnetic bead for 3 hrs and left for 24 hrs. Then the solution was filtered through (0.45 µm Whitman filter) and the filtrate was examined for the drug content using UV- visible spectrophotometer at λ_{max} (273nm) in triplicate.[16],[17]

Mechanical Characteristics

The physical mechanical properties of the films were determined through the standard test method for tensile properties of thin plastic sheeting by the American Society for Testing and Materials (ASTM),[18] the sample was cut into a dumbbell shape as shown in Fig.1. The mechanical properties include tensile strength (TS) and percentage elongation at break (%EB). The following equations were used to calculate the TS and %EB:

$$\textbf{Tensile strength} = \frac{\text{Force at break (N)}}{\text{Initial cross- sectional area of the sample}} \qquad \textbf{eq. (1)}$$

$$\%EB = (D_f - D_0/D_0) \times 100 \qquad \textbf{eq. (2)}$$

Where **%EB** = Percentage elongation at break, $\mathbf{D_0}$ = Distance between the tensile grips before the fracture of the film, $\mathbf{D_f}$ = Distance between the tensile grips after the fracture of the film.

Film strip with the dimensions (10-12 x 1.5-2) cm and free from air bubbles or physical inadequacies, were held between two clamps, the upper one is moveable and the lowered one is fixed, the test was done with a head speed of 10 mm/min. with a cell load 50 kN.

Fig.1: Sample Cut into Dumbbell Shape for Mechanical Properties Estimation and Photographs of Texture Analyzer Instrument While Measuring the Mechanical Properties.

Swelling Index (water uptake)

A patch of 2x2 cm^2 size was weighed on a preweigh microscope slide. A 50 ml phosphate buffer pH 6.8 was added to a petridish containing the patch over the microscope slide. At regular time intervals for 60 min, the microscope slide was removed and weighed. The difference in weights gives the weight increase due to absorption of buffer and swelling of patch is calculated by the following equation:

Swelling Index = (W_2-W_1/ W_1) x 100% **eq. (3)**

Where, W_1 is the weight of buccal patch before dipping into phosphate buffer pH 6.8 and W_2 is the weight of buccal patch after dipping in phosphate buffer pH 6.8 and wiped with filter paper.[19]

Measurement of Mucoadhesive Strength

A modified physical balance was used for determining Ex-Vivo mucoadhesive strength. Fresh chicken pouch was gotten from slaughterhouse and used as a model mucosal memebrane.[20] It was used within 2 hrs of slaughter, the membrane was washed with phosphate buffer pH 6.8 and stuck on the bottom of the petridish by cyanoacrylate glue such that the mucosal surface faces upwards and the phosphate buffer is added till the buffer reaches the surface of mucosal membrane and keeps it moist. The buccal patch was stuck to the lower side of glass stopper with cyanoacrylate glue which is hanged from the balance left arm by threads after removing its pan,[21] The two sides of physical balance were made equal

before the study, by keeping 5 gram weight on the right hand pan, a weight of 5 gram was removed from the right hand pan, which let down the glass stopper along with the patch over the mucosa. The balance was kept in this position for 10 min, a weight was applied to the right pan by adding water drop by drop to a beaker till complete detachment of the patch achieved. The mucoadhesive strength (bioadhesive strength) represents the amount of water added minus the weight of the preload, force of adhesion and bond strength were calculated from the following equations.[22]

Force of adhesion (N) = Bioadhesive strength × 9.8 / 1000 **eq. (4)**

Bond strength (N/m2) = Force of adhesion (N) / surface area **eq. (5)**

***Ex-Vivo* Residence Time**

The mucoadhesive performances of mucoadhesive patches were evaluated by estimating the time for these patches to detach from chicken pouch membrane in a well-stirred beaker, the chicken pouch membranes were fixed on the side of the beaker with cyanoacrylate glue and one side of each patch was wetted with 1 drop of phosphate buffer pH 6.8 and the patches were attached to the membrane by applying light force with fingertip for 60 seconds.[23] Then 500 ml phosphate buffer pH 6.8 was added to the beaker at 37 ˚C. A stirring rate of approximately 150 rpm were used to simulate buccal and saliva movement. The time required for complete erosion or detachment of the patches from chicken pouch membrane was considered as indication of Ex -Vivo adhesion time.[24]

Percentage Moisture Absorption and Percentage Moisture Loss

The percentage moisture absorption (PMA) test was carried out to check the physical stability of the buccal patch at high humid conditions. In the present study the moisture absorption capacity of the patches were determined as follows: Three 1cm diameter patches were cut out and weighed accurately. The patches were placed in desiccator containing saturated solution of aluminum chloride, keeping the humidity inside the desiccator at (79.5-80 %). After 3 days each patch was removed, weighed and percentage moisture absorption was calculated by applying the following equation.[25] The average percentage of the three patches was recorded

PMA= ((Final weight – Initial weight)/ Initial weight) x 100 **eq. (6)**

The percentage moisture loss (PML) was calculated to check the integrity of patch at dry condition. Three 1cm square patches were cut out and weighed accurately and kept in

desiccators containing fused anhydrous calcium chloride. After 72 hrs, each patch was removed and weighed.[26] The percentage moisture loss was calculated by using formula:

PML= ((Initial weight – Final weight) / Initial weight) x 100 eq. (7)

The average PML of three patches was recorded.

***Invitro* Release Study**

The drug release from buccal patches was studied using USP dissolution apparatus type II, it was thermostated at the temperature of 37 ± 0.5 °C and stirred at rate of 50 rpm. Each patch (2x2 cm^2) was fixed on a glass slide with the help of cyanoacrylate adhesive in such a way that the mucoadhesive layer was in contact with dissolution medium and non-adhesive backing layer fixed on the glass slide, then the slide was immersed in the vessel containing 500 ml of phosphate buffer solution pH 6.8,[27] the glass slide acts as a support to prevent floating of the patch and settle the dosage form in the bottom of the jar. The aliquots of 5 ml were withdrawn at predetermined time interval 15, 30, 60, 120, 180, 240, 300, 360 min and replaced with equal volumes of the dissolution medium equilibrated at the same temperature to maintain sink condition. Drug concentration of the withdrawn samples was analyzed after filtration (0.45 µm Whitman filter) by UV-visible spectrophotometer at λ_{max} (273 nm).

***Invivo* Drug Release Test**

Invivo release test was performed by applying optimized film to five healthy volunteers' buccal mucosa. Volunteers were instructed to press the film for 60 seconds, the volunteers did not take water and food half an hour before the study and continued fastening during all the experiment. An optimum formula were placed in the buccal cavity, one patch for each time interval 30,60,120,180,240,300,360 min then the patch was taken out at the end of each interval. The process was repeated three times to validate the results, each patch was dissolved in 100 ml of phosphate buffer pH 6.8 and the drug remained unreleased was spectrophotometrically analyzed at λ_{max} (273 nm). The result were subtracted from amount of drug present in patch, which represent the amount released from the buccal patch.[28],[29]

Characterization of Selected Formula Using SEM

Patch morphology was characterized by scanning electron microscopy (SEM); the sample of selected formula was fixed on round brass stubs with using double backed adhesive tape and then sputter coated for 30 seconds with gold palladium under an argon atmosphere before

examination under the SEM, Afterwards, the stub containing the coated samples was placed in the SEM chamber.

Accelerated Stability Studies

This study was done at accelerated thermal conditions (40, 50 and 60 $^{\circ}$C), the selected formulas stored in the ovens for three months, samples were taken every 2 weeks intervals and the content of MCP HCl was measured using UV absorbance at λ_{max} (273nm).

Statistical Analysis

Statistical analysis was done by using one - way analysis of variance (ANOVA). The differences are statistically significant when ($p < 0.05$).

RESULT AND DISSCUSION

Physical Evaluation

The results in table (2) showed that all the formulated patches had uniform weight ranged (150.35-177.50) however changing plasticizer type from PG (F4) to PEG 400 (F6) led to significant increase ($p < 0.05$) in the weight this may be due to the high molecular mass of PEG 400 when compared to PG,[30] all formulas showed thickness ranged (0.234-0.590) mm and folding endurance > 300, the surface pH of the formulas are within the limits of salivary pH and ranged (6.21-6.88) except for formulas containing carpabol (F7- F9) in which there are significant decrease ($p < 0.05$) in surface pH this is likely due to acidic group present in the structure of carpabol might have decreased the pH and resulted in an increase of irritation.[31]

Content Uniformity

All the prepared patches were found to contain uniform quantity of the drug; the preparations met the criteria of USP content uniformity (90-110 % of the label claim). The results of content uniformity studies indicated reproducibility of the technique used.

Table (2): Results of Physical Evaluation Parameters of Prepared MCP HCl Mucoadhesive Buccal Patches.

Formula No.	Uniformity of weight (mg)	Thickness (mm)	Folding endurance	Surface pH	Content uniformity (%)
F1	159.14±8.12	0.234±0.032	>300	6.51±0.13	92.32±0.028
F2	151.58±9.32	0.244±0.057	>300	6.23±0.11	91.70±0.023
F3	154.38±3.45	0.276±0.011	>300	6.76±0.02	104.48±0.045
F4	158.93±2.13	0.296±0.028	>300	6.82±0.24	90.63±0.051
F5	157.62±1.46	0.454±0.012	>300	6.21±0.06	107.46±0.007
F6	177.50±1.12	0.590±0.045	>300	6.67±0.14	95.20±0.047
F7	150.35±1.82	0.263±0.021	>300	3.68±0.13	95.55±0.013
F8	155.16±2.54	0.247±0.004	>300	3.83±0.11	93.84±0.005
F9	160.71±3.78	0.259±0.013	>300	3.97±0.16	101.09±0.035
F10	157.21±3.98	0.265±0.033	>300	6.88±0.14	94.61±0.015
F11	161.56±4.20	0.267±0.055	>300	6.76±0.05	99.05±0.041
F12	163.11±3.65	0.278±0.043	>300	6.57±0.01	93.01±0.038

Mechanical Characteristics

The TS gives an indication of the strength and elasticity of the patch. Table (3) revealed that The TS and %EB of the patches found to vary with the nature of polymer and plasticizer type. Incorporation of secondary polymers PVP (F2-F4), Carpabol (F7-F9) resulted in significant decrease ($p < 0.05$) in TS and increase in %EB as their amount increased while formulas containing Na CMC (F10-F12) resulted in significant decrease ($p < 0.05$) in both TS and %EB as the amount of Na CMC increased this resulted this may be due to decreased crosslinking between these two polymers.[32]

Changing plasticizer type into PEG 400 (F6) showed different mechanical properties than the PG (F4) and glycerin (F5). There is significant increase ($p < 0.05$) in both TS and %EB for (F6) this is may be due to the fact that PEG 400 has higher molecular weight than glycerin and PG, the longer carbon chain exhibit greater flexibility and elasticity, thus they can extended further before ruptured as compared with short chain one,[33] Formula F4 produces higher TS and less elongation than F5 and the reason behind this is probably due to the presence of a hydrophobic group on the plasticizer (PG), resulting in a specific orientation of the molecules within the polymer structure.[34]

Table (3): Mechanical Properties of Prepared MCP HCl Mucoadhesive Buccal Patches.

Formula NO.	(TS) MPa	% EB
F1	16.71	18.43
F2	8.13	27.31
F3	13.79	26.91
F4	15.34	26.75
F5	11.72	27.80
F6	24.36	28.10
F7	4.41	37.40
F8	6.48	31.24
F9	6.67	28.76
F10	8.5	16.87
F11	14.7	18.43
F12	16.34	20.1

Swelling Index

Table (4) revealed that incorporation of hydrophilic secondary polymers PVP, Na CMC and Carpabol into HPMC K4M resulted in increase of swelling index as the amount of polymer increased and being the highest in F7 which contained the highest amount of Carpabol this is due to ionization of carboxylated group of Carpabol at the pH environment of the experiment, which led to development of negative charges along the back bone of polymer, repulsion of the like charges uncoil the polymer into an extended structure. The counter ion diffuses inside the gel creates an additional osmotic pressure differences across the gel leading to a considerable swelling of the polymer.[35] The swelling index of patch contained PEG 400 (F6) is significantly higher ($p < 0.05$) than the patch contained glycerin (F5) and PG (F4) as plasticizer. This could be due to the higher water uptake of PEG 400, which may alter the water distribution within such system.[36]

Mucoadhesive Strength

A successful buccal mucosal delivery device must maintain intimate interaction with mucus layer covering the epithelial tissue. This feature is very critical for effective utilization of such devices. The mucoadhesive strength values were found between (49.56 - 18.56) gm as shown in table (5). The incorporation of secondary polymers PVP, Na CMC and carpabol led to increase in mucoadheive strength and it was increased as the amount of polymer increased. The highest value of mucoadhesive force was recorded for (F7) and it is attributed to carpabol probably due to formation of strong gel by formation of hydrogen bonding.[37] Utilizing glycerin as plasticizer (F5) led to higher mucoadhesive strength than other types. This significant differences ($p < 0.05$) could be attributed to the differences in the chemical

structure between the plasticizers, which played a major factor in the consolidation process of mucoadhesion (capability of hydrogen bond formation) with the mucus.[38]

Table (4): Swelling Index of Formulated MCP HCl Buccal Patches.

Formula No.	10 min	20 min	30 min	40 min	50 min	60 min
F1	8.81	11.02	13.09	14.40	15.88	17.58
F2	11.96	14.65	16.31	17.56	19.98	23.80
F3	10.03	12.40	13.93	15.17	17.17	20.59
F4	9.95	11.93	13.78	14.60	16.09	18.64
F5	11.39	17.81	21.59	23.22	25.67	27.57
F6	14.65	18.99	23.19	26.53	29.61	30.08
F7	15.21	28.58	35.84	37.43	38.44	40.23
F8	10.66	15.74	21.14	29.31	33.31	36.71
F9	8.76	13.95	17.44	18.84	20.73	27.23
F10	11.21	19.39	27.88	31.16	32.26	34.08
F11	10.06	13.65	15.81	20.56	24.98	27.80
F12	8.34	12.34	14.61	18.13	20.60	22.65

Table (5): Mucoadhesive Strength and Ex-Vivo Residence Time of Prepared MCP HCl Patches.

Formula No.	Bioadhesive strength (gm)	Force of adhesion (N)	Bond strength (Nm^{-2})	Ex-vivo residence time (hrs)
F1	18.56 ± 0.154	0.181	454.72	7.31 ± 0.65
F2	23.37 ± 0.478	0.229	572.56	5.31 ± 0.32
F3	20.8 ± 0.035	0.203	509.60	6.09 ± 0.43
F4	19.26 ± 0.014	0.188	471.87	6.23 ± 0.21
F5	23.37 ± 0.025	0.229	572.56	6.86 ± 0.32
F6	19.64 ± 0.198	0.192	481.18	6.37 ± 0.43
F7	49.56 ± 0.479	0.485	1214.22	> 12
F8	44.03 ± 0.743	0.431	1078.73	> 12
F9	39.21 ± 0.467	0.384	960.64	> 12
F10	24.81 ± 0.346	0.243	607.84	4.56 ± 0.32
F11	21.23 ± 0.198	0.208	520.13	4.89 ± 0.56
F12	20.03 ± 0.568	0.196	490.73	5.16 ±1.21

***EX-Vivo* Residence Time**

The longest adhesion time was observed for formulas containing carpabol (F7-F9) being more than 12 hrs, this is may be due to its high mucoadhesive nature and interpenetration of polymeric chains in the mucus membrane.[39] While for other formulas there was no correlation found between bioadheion force and residence time of polymer, it seem that highly bioadhesive polymer do not necessarily reside longer on mucoadhesive surface. Surface charge density and chain flexibility are considered to be a prerequisite for bioadhesion, whereas residence time is primarily dependent on the dissolution rate of the

polymer,[40] this was observed when PVP and Na CMC was added to HPMC (F2-F4) and (F10-F12) respectively, where shorter residence time was observed as the amounts of PVP and Na CMC were increased.

Percentage Moisture Absorption and Percentage Moisture Loss

From the results listed in table (6) the percentage moisture absorption and percentage moisture loss were increased with increasing amounts of hydrophilic secondary polymers PVP, Na CMC and Carpabol, F7 which contains the highest amounts of Carpabol showed significantly higher ($p < 0.05$) PMA than other types of polymers this could be due to swelling of Carpabol and hold more amount of water in its network as it is more hygroscopic in nature.[41] For formulas containing different plasticizers the results of PMA and PML showed that F6 >F5 >F4. Formula (F6) contained PEG 400 showed the highest value due its hygroscopic nature and has the ability to absorb water. Formula (F6) which contained glycerin showed significant increase ($p < 0.05$) in PMA than F5 which contained PG since glycerin is a highly hydrophilic plasticizer and combines with high affinity to water.[42] None of patches lost their integrity during the PMA and PML study.

Table 6:- Percentage Moisture Absorption and Percentage Moisture Loss of Prepared MCP HCl Mucoadhesive Buccal patches.

Formula NO.	Percentage moisture Absorption (PMA)	Percentage moisture loss (PML)
F1	4.89 ± 0.54	4.12 ± 0.98
F2	8.68 ± 0.77	6.32 ± 0.99
F3	7.31 ± 0.65	5.85 ± 0.71
F4	5.35 ± 0.73	4.81 ± 0.41
F5	22.52 ± 0.82	17.41 ± 0.45
F6	24.46 ± 0.09	21.42 ± 0.89
F7	14.2 ± 0.56	12.10 ± 0.14
F8	11.65 ± 0.21	10.91 ± 0.47
F9	11.21 ± 0.51	10.21 ± 0.29
F10	9.14 ± 0.71	7.65 ± 0.48
F11	8.98 ± 0.21	7.22 ± 0.26
F12	7.14 ± 0.59	6.67 ± 0.57

***Invitro* Drug Release**

Fig.2 and Fig.3 showed that the incorporation of hydrophilic secondary polymers PVP and Na CMC into HPMC resulted in increase of drug release as the amount of polymer increased in which PVP produce higher *invitro* drug release than Na CMC, while incorporation of Carpabol resulted in significant decrease ($p < 0.05$) in drug release as shown in Fig.4. This is

due to increase the thickness of the gel layer as the amount of carpabol increased which in turn inhibit water penetration and consequently resulted in further reduction in drug release as the amount of polymer increased.[43] The effect of plasticizer type on the release of MCP HCl from formulas (F4-F6) was studied. It was observed that changing the plasticizer type had non-significant differences ($p > 0.05$) on the drug release profile of MCP HCl, the order of drug release is PG > glycerin > PEG 400. This could be explained that the presence of PG in the preparation helps the solution to be more hydrophilic and can increase the partition coefficient; and so can increase the diffusion of drug through different mechanisms.[44]

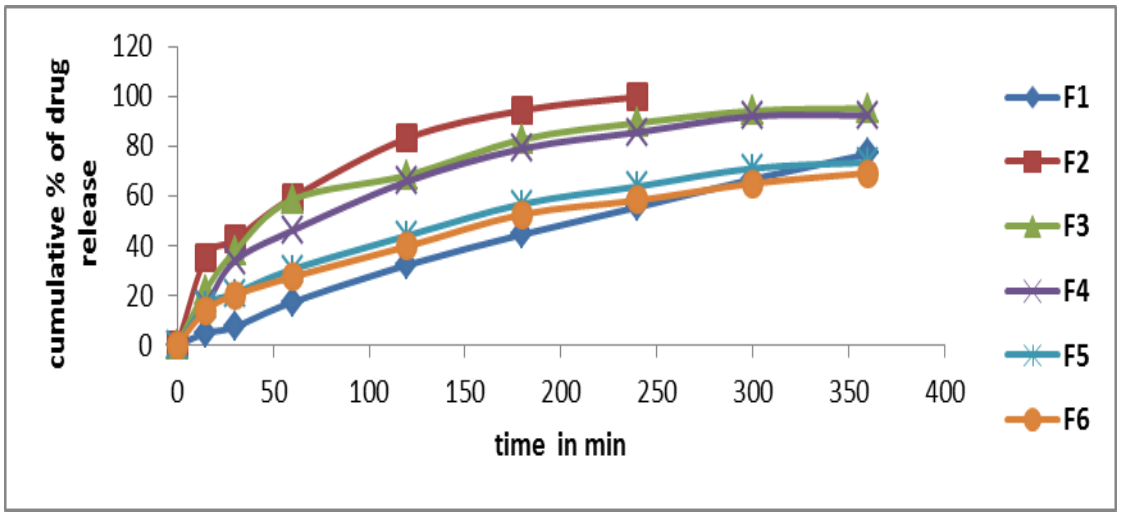

Fig. 2: Effect of incorporation of PVP into HPMC (F2-F4) and changing plasticizer type (F5-F6) on *Invitro* release of MCP HCl in phosphate buffer pH 6.8 at 37 °C from mucoadhesive buccal patches.

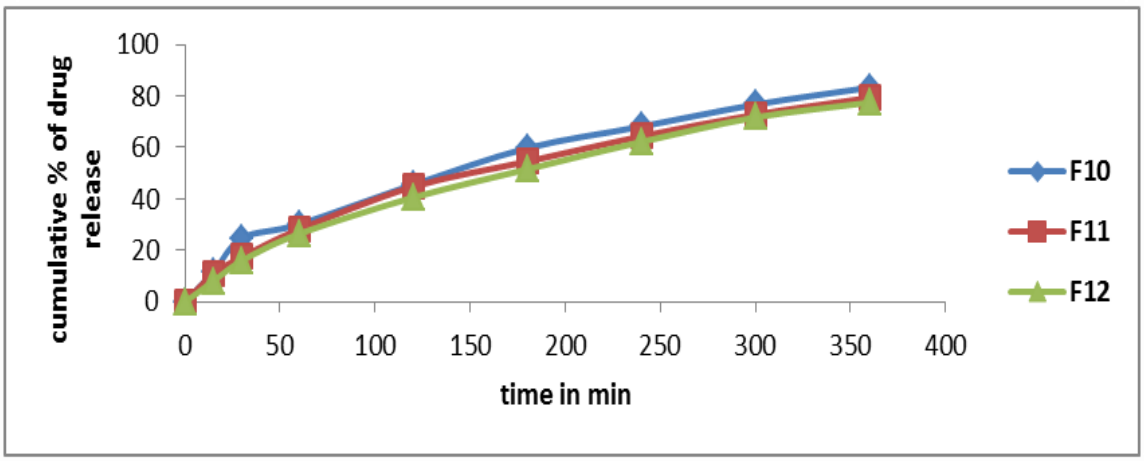

Fig.3: Effect of incorporation of Na CMC into HPMC on invitro drug release of MCP HCl in phosphate buffer pH 6.8 at 37 °C from mucoadhesive buccal patches.

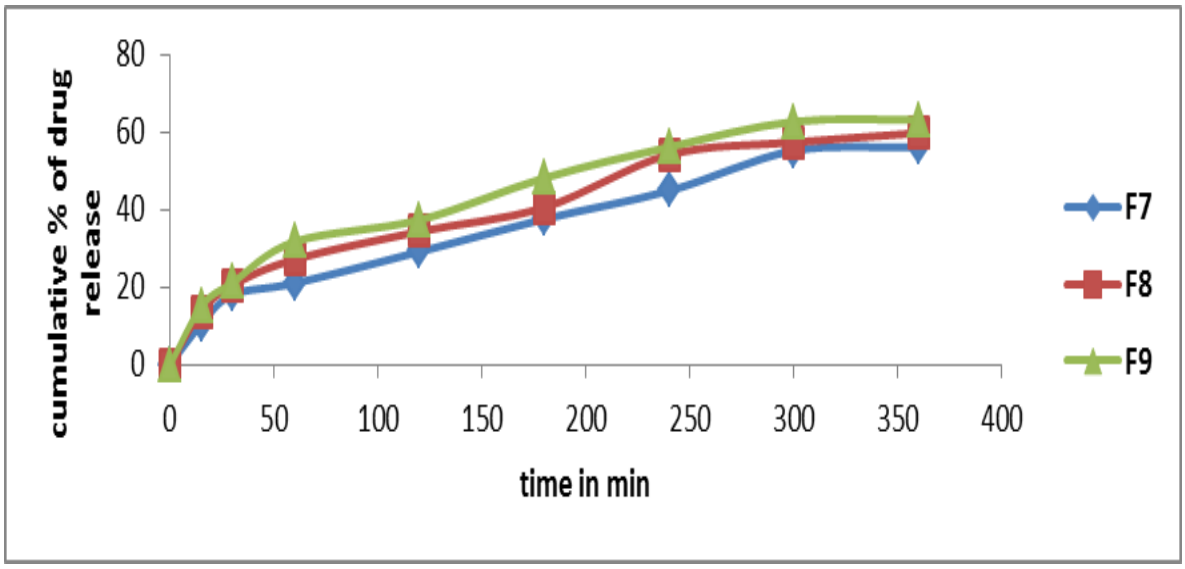

Fig. 4: Effect of incorporation of Carpabol into HPMC on *invitro* drug release of MCP HCl in phosphate buffer pH 6.8 at 37 °C from mucoadhesive buccal patches.

Determination of Selected Formula

Formula F4 was chosen as selected formula and picked for further investigations; the patch had accepted value for mechanical properties, surface pH, good swelling index, convenient mucoadhesive strength and suitable *Ex-Vivo* residence time with high drug release after 6 hrs as shown in table 8.

Table 8:- Properties of selected formula of MCP HCl mucoadhesive buccal patches.

Parameter	F4
Tensile strength (MPa)	15.34
Elongation of break %	26.75
Swelling index(60 min)	18.64
Mucoadhesive strength (gm)	19.23
Ex-Vivo Residence time (hrs)	6.23
Percentage moisture absorption (3 days)	5.35
Percentage moisture loss (3 days)	4.81
Cumulative amount of drug release %	92.34
Folding endurance	> 300
Surface pH	6.82 ± 0.24

***Invivo* Drug Release**

The selected formula (F4) was chosen for *invivo* test on human buccal cavity, the method used for determining the *invivo* release is the method of disappearance of the drug from the patches. It was found that 69.54 % of MCP HCl released after 6 hrs, as shown in Fig.5. The patches did not cause any discomfort or irritation to the volunteers and no side effects like

heaviness, dry mouth or severe salivation were observed. The system claims the potential clinical usefulness in delivering the drug.

***Invivo -Invitro* correlation (IVIVC)**

The result of (IVIVC*)* was found to have acceptable correlation with (R^2) value of (0.9822) as shown in Fig. 6.

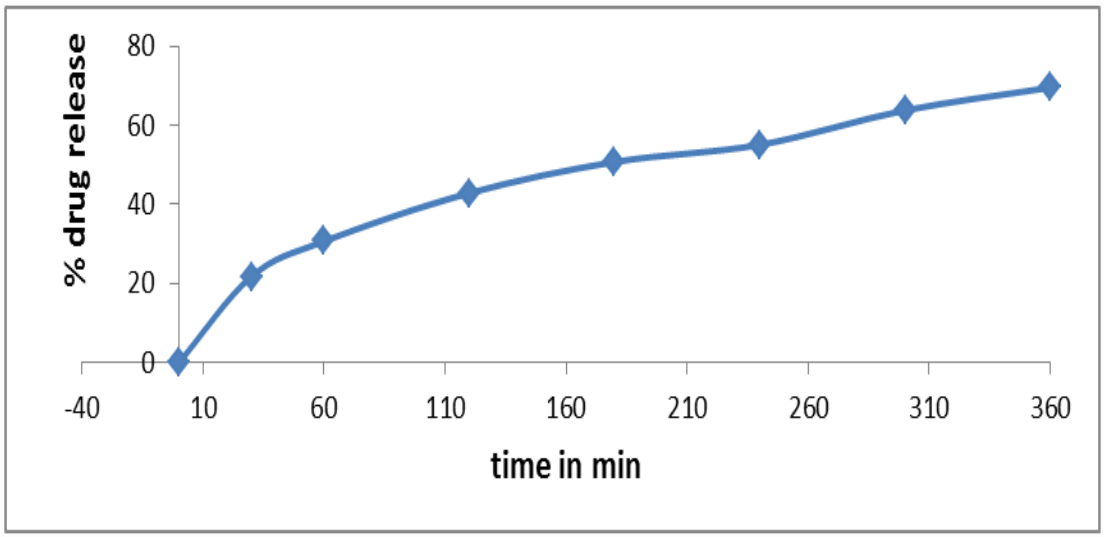

Fig. 5: *Invivo* release of MCP HCl from buccal patches in human volunteers' buccal cavity for selected formula F4.

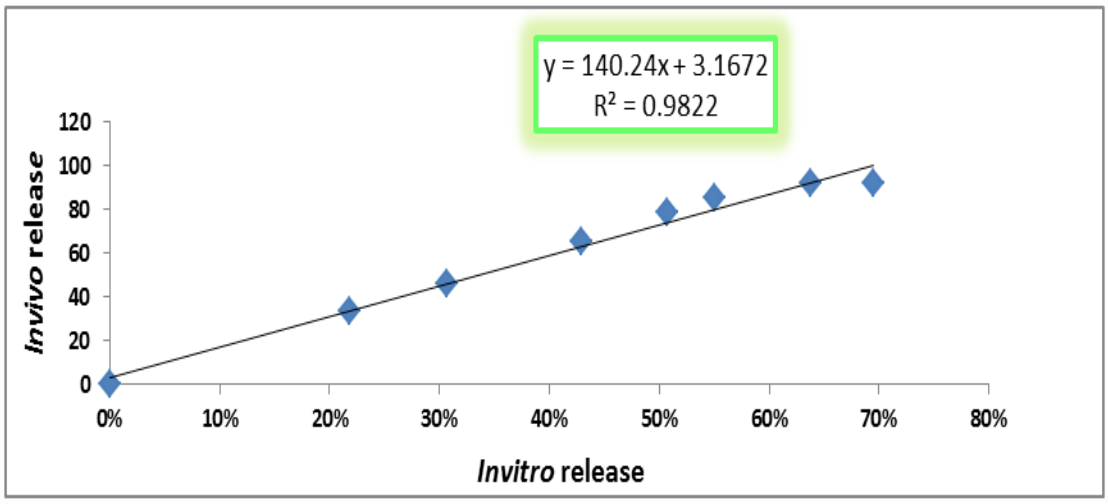

Fig. 6: *Invito - Invivo* release correlation of MCP HCl From buccal patch for selected formula F4.

Characterization of Selected Formula Using SEM

The cross sectional and surface SEM microphotographs of the selected mucoadhesive buccal patch (F5) is shown in Fig. 7, there were no crowded crystals in one place indicating uniform distribution of the content within the patch.

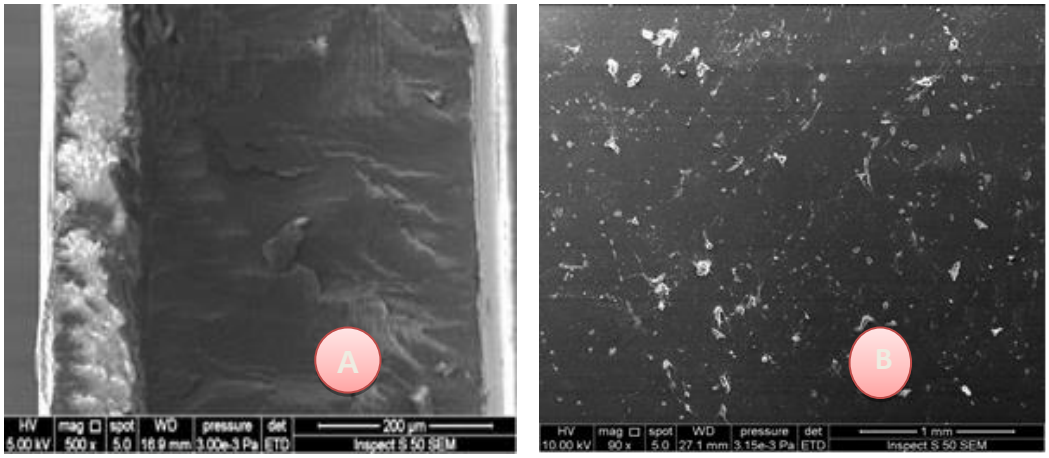

Fig. 7: (A) Cross sectional SEM photograph, (B) Surface SEM photograph of mucoadhesive buccal patch of selected formula F4.

Accelerated Stability Study: Determination of Expire Date

The expiration date of the selected formula (F4) was calculated at 25 ºC and was found to be 2.9 years indicating the stability of the drug in the formulated patch.

CONCLUSION

The overall study revealed that metoclopramide HCl can be formulated as bilayer mucoadhesive buccal patch by using HPMC K4M as primary polymer and PVP secondary polymer and ethyl cellulose as backing layer that extend the drug release through the buccal mucosa for 6 hrs .

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