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Research Article

Formulation Development and Evaluation of Combinational Buccal Patches Containing Esomeprazole Magnesium Trihydrate and Metoclopramide Hydrochloride

S RAJA SUNDARAM*, K RAMESH KUMAR, S SUDHARSAN, S NAVEEN KUMAR

Department of Pharmaceutics, College of Pharmacy, Madras Medical College, Chennai-600 003, Tamil Nadu, India.

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ABSTRACT

The prime objective of the present study was to formulate and evaluate buccal patches containing combination of Esomeprazole Magnesium Trihydrate and Metoclopramide Hydrochloride. The buccal films were fabricated by solvent casting method using mucoadhesive polymers such as Hydroxy Propyl Methyl Cellulose (HPMC), Hydroxy Propyl Cellulose (HPC), Poly Vinyl Alcohol (PVA), Poly Vinyl Pyrolidone (PVP) and ethyl cellulose as a backing layer. The prepared patches were evaluated for various physicochemical properties such as weight, thickness, surface Ph, folding endurance, bioadhesive strength, water uptake, moisture loss, drug content, elongation at break, *in-vitro* release studies and release kinetics studies. The IR spectra showed no interaction between drugs and polymer. The physicochemical characteristics of all the samples were found to be satisfactory. The water uptake of the films increase with increase in the content of HPMC,HPC and PVA. The percentage elongation, bioadhesive force and folding endurance of the film increased with increase in the concentration of HPMC. The *in-vitro* drug release demonstrated slower release of both drugs in formulations with higher proportion of HPMC and HPC. The *in-vitro* drug release data of the optimized formulation best fitted zero order model. Buccal delivery of this combination can resolve the draw backs of first pass metabolism in the stomach and thereby possibly improve the bioavailability.

INTRODUCTION

Buccal adhesive films are new drug delivery system, which are made by using muco-adhesive polymer. Buccal films can be defined as a dosage form that employs a water dissolving polymer, which allows the dosage form to quickly hydrate, adhere and dissolve when placed on the tongue, or in the oral cavity which results in systemic circulation. Buccal films are considered due to their flexibility, comfort and the relatively long residence time on the mucosa. The muco adhesive film can be bi-layer for unidirectional release and prevent absorption from Gastro Intestinal Tract. Buccal films have direct access to the systemic circulation through the internal jugular vein, which bypasses the drug from the hepatic first pass metabolism leading to high bioavailability. The main property of the buccal film is that due to the large surface area of the film, it allows quick wetting of the film which accelerates absorption of the drug. [1 - 3]

Advantages [4, 5]

1. The buccal delivery benefits by more blood supply towards oral cavity.
2. First pass effect avoided because drugs directly absorbed from oral mucosa.
3. The usage of buccal dosage forms is easier than others. They can be discontinued if toxic effects appeared.
4. The side effects decreased and improved patient compliance.
5. The peptide molecules that not suitable for delivering through oral route can easily administered by buccal mucosa.
6. Buccal delivery system has a capacity to withstand environmental conditions and sustained delivery of drugs possible.

Disadvantages [6]

1. The dilution of the drug takes place by the uninterrupted excretion of the saliva.

Author for Correspondence:
Email: rajsp4202@gmail.com

2. Drugs with large potency dosage are problematic to be given by buccal route.
3. The unintentional removal of dosage form happens by incessant swallowing of saliva probable loss of medication.
4. Lesser area of the oral cavity available for drug absorption.
5. Drugs which annoy the mucosa or have an acrimonious flavor not appropriate.
6. Barrier properties of the mucosa.
7. Drugs which are unstable at buccal pH cannot be administered.

MATERIALS AND METHODS

Esomeprazole Magnesium Trihydrate was provided by saimirra inno pharm. Chennai. Metoclopramide hydrochloride was provided by ipca laboratories. Chennai.

Hydroxy Propyl Methyl Cellulose E 15 , Hydroxy Propyl Cellulose , Poly Vinyl Alcohol , Poly Vinyl Pyrolidone and Ethyl Cellulose were provided by saimirra inno pharm. Chennai.

Propylene glycol were provided by fourrts india laboratories. All other chemicals / reagents used were of analytical grade.

Dose Calculation of Esomeprazole Magnesium Trihydrate [7]

- The amount of dug present in one film = 20 mg ofEsomeprazole Magnesium Trihydrate
- Diameter of the proposed film = 2 cm^2
- Area of the proposed film =4 cm
- Diameter of the glass plate = 8 cm^2
- Area of the plate = 64 cm
- Number of films present in proposed area of the plate = 64/4 =16 films
- For this purpose the concentration of drug in formulation should be 320 mg.

Dose Calculation of Metoclopramide Hydrochloride

- The amount of dug present in one film = 10 mg of Metoclopramide Hydrochloride
- Diameter of the proposed film = 2 cm^2
- Area of the proposed film = 4 cm
- Diameter of the glass plate = 8 cm^2
- Area of the plate = 64 cm
- Number of films present in proposed area of the plate = 64/4 =16 films
- For this purpose the concentration of drug in formulation should be 160 mg.

Preparation of Buccal Patches [8, 9]

Patches containing Esomeprazole Magnesium Trihydrate and Metoclopramide Hydrochloride and HPMC E15, HPC, PVA different proportions with PVP was prepared by the solvent casting method. The drug was dissolved in 5mL of ethanol and the polymers were dissolved in separate container with 20mL of distilled water under continuous stirring for 4 hours. After stirring, mix the drug and polymer solution. Propylene Glycol was added into the solution as a Plasticizer under constant stirring and the Dimethyl sulphoxide added as a Penetration enhancer. The viscous solution was left over night to ensure a clear, bubble free solution. The solution was poured into a glass petridish and allowed to dry at 40°C temperature till a flexible patch was formed. Dried patch was removed carefully, checked any imperfections or air bubbles and cut into pieces of 2×2 cm area. The buccal patches were supported by backing layer which was again prepared. The compositions of patches were tabulated.

Preparation of Backing Layer

The backing membrane was prepared by dissolving 200mg of Ethyl Cellulose in 10mL of ethanol and mixed well. 1mL of Propylene Glycol was added then and mixed well.

Table 1: Formulations of Buccal Patches

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Esomeprazole Magnesium Trihydrate (mg)	320	320	320	320	320	320	320	320	320
Metoclopramide Hydrochloride (mg)	160	160	160	160	160	160	160	160	160
HPMC (mg)	240	320	400	-	-	-	-	-	-
HPC (mg)	-	-	-	240	320	400	-	-	-
PVA (mg)	-	-	-	-	-	-	240	320	400
PVP (mg)	240	160	80	240	160	80	240	160	80
Dimethyl sulphoxide(mL)	2	2	2	2	2	2	2	2	2
Propylene Glycol(mL)	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Ethanol(mL)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Distilled water(mL)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

The solution was kept aside for overnight and dried films were collected. The patches were packed in an aluminium foil and stored in desiccators to maintain the integrity and elasticity of the patches.

Evaluation of Combinational Buccal Patches

a) Thickness of Patch:

Thickness of patch was measured at different randomly selected spots using screw gauge. The mean and standard were calculated.

b) Folding Endurance:

Folding endurance of the buccal patches was determined by taking 20mm diameter of patch was repeatedly folding at the same place till it broke. The no of times of patch could be folded at the same place without breaking gave the value of the folding endurance. The test was done three times and calculates the mean and standard.

c) Weight Variation Test

The weight variation test was carried out by weighing five films individually using digital balance. The mean weight of film was noted.

d) Surface pH

The surface pH of the patches was determined in order to investigate the possibility of any side effects due to change in pH *in- vivo*, since an acidic or alkaline pH may cause irritation to the buccal mucosa. The patch to be tested was placed in petridish and was moistened with 0.5mL of distilled water and kept for 30 seconds. The pH was noted after bringing the electrode of pH meter in contact with the surface of the formulation and allowing equilibrating for 1 min.

e) Percentage Moisture Loss Test [10]

Percentage moisture loss test was determined by keeping the films in a dessicator containing anhydrous calcium chloride. After 3 days, the films were taken out, reweighed and the percentage moisture loss was calculated using formula:

$$\% \text{ Moisture Loss} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} X100$$

f) Water Uptake Study [11]

The moisture uptake studies give an indication about the relative moisture absorption capacities of polymers and an idea whether the formulations maintain their integrity after absorption of moisture. This test was carried out by dissolving 5% w/v agar in hot water. It was transferred into petriplates and it was allowed to solidify. Six drug free patches from each formulation were selected and weighed. They were placed in vacuum oven overnight prior to the study to remove moisture if any and laminated on one side with water impermeable backing membrane. They were then incubated at 37°C for one hour, removed and reweighed. The Percentage moisture absorption was calculated by using the formula:

$$\%\text{Water uptake} = \frac{\text{Final weight - Initial weight}}{\text{Initial weight}} X100$$

g) Percentage Elongation Test [12]

When stress is applied to a sample piece, strain develops and the length of the sample increases with increase in the amount of stress applied. The point at which the sample piece breaks after a sufficient increase in length is referred as percent elongation break.

$$\% \text{ Elongation} = \frac{\text{Increase in length of film}}{\text{Initial length of the film}} \times 100$$

h) *Ex-vivo* Bioadhesion Method [13]

A piece of gingival mucosacuteroded with phosphate buffer (6.8) and knotted with open mouth glass vial. The glass vial is tightly fitted with phosphate buffer. The temperature of the apparatus maintained at 37°C±1°C and touching the mucosal surface. Cyanoacrylate adhesive used to fixed patch and balance are well adjusted with weight that of five gram. The weight which loaded in the left hand side pan fastened with the patch over the mucosa removed, the contact time of patch is 5 minutes. Hundred drops per minute water are added to the right hand side pan gradually until the patch removed from the mucosal surface. The magnitude of mucoadhesive strength required to separate the patch from the mucosal surface concluded by weight in grams.

i) Drug Content Uniformity

Drug content uniformity was calculated by taking three film units of each formulation were taken in separate 100mL volumetric flasks, 100mL of phosphate buffer pH 6.8 was added and continuously stirred for 24 hrs. The solutions were filtered, diluted suitably and analyzed at 302nm and 273nm in a UV spectrophotometer. The average of drug contents of three films was taken as final reading.

j) *In -Vitro* Release Studies [14 -16]

In-vitro release studies were carried out by slight modification of the method suggested by Perioli L *et al* and Ilango *et al.* A buccal patch was attached to the wall of the dissolution vessel such as a 250mL beaker midway from the bottom with instant adhesive. After 2 min the vessel was filled with 200mL of phosphate buffer of pH 6.8 and placed on a magnetic stirrer. The temperature of the dissolution medium was maintained at 37°C and stirred at 50 rpm. Samples of 5mL were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were diluted appropriately with simulated saliva and assayed spectrophotometrically at 302nm and 273nm by simultaneous estimation method. Three patches of each formulation were subjected to drug release studies in the same manner and the average cumulative percentage drug was determined.

k) Stability Study [17,18]

The stability studies of Esomeprazole Magnesium Trihydrate and Metoclopramide Hydrochloride buccal patches were conducted to evaluate physical appearance, surface pH, folding endurance and *in-vitro* drug release at the end of 30 days when stored under conditions at 40°C±2°C / 75%±5% RH.

RESULTS AND DISCUSSION

Table 2: Physical parameters of formulations F1 – F9.

Formulation Code	Physical parameters							
	Thickness	Folding Endurance	Water uptake	Uniformity of Weight	Surface pH	Percentage Moisture Loss	% Elongation	Bioadhesive strength (gms)
F1	0.05±0.003	284±10	3.07	0.061±0.005	6.55±0.02	2.43	40%	169.34±2.13
F2	0.05±0.004	279±10	4.24	0.074±0.006	6.81±0.02	5.08	45%	177.67±0.78
F3	0.06±0.002	294±10	4.28	0.070±0.004	6.75±0.03	5.97	45%	186.28±0.98
F4	0.06±0.003	286±10	2.70	0.071±0.003	6.54±0.04	4.10	40%	157.33±1.34
F5	0.07±0.003	289±10	2.94	0.068±0.005	6.90±0.02	2.94	40%	164.64±3.67
F6	0.08±0.002	302±10	2.89	0.072±0.003	6.73±0.02	7.10	45%	169.23±2.87
F7	0.06±0.004	277±10	1.28	0.081±0.005	6.67±0.03	3.70	40%	142.35±1.74
F8	0.07±0.002	269±10	1.58	0.065±0.004	6.52±0.03	2.89	40%	153.23±1.53
F9	0.08±0.003	271±10	2.66	0.071±0.005	6.64±0.02	4.20	40%	144.46±1.13

Table 3: Stability data for optimized formulation

Stability Condition		Physical Appearance		Folding Endurance	
		Initial	After 30 days	Initial	After 30 days
40±2°C /75±5%RH	F3	NC	NC	294	279

NC- No Change

Time (hours)	Cumulative % Drug Release			
	40±2°C/75±5%RH			
	F3 (EMT)		F3 (MH)	
	Initial	After 30 days	Initial	After 30 days
1	8.57	8.47	7.83	7.78
2	18.28	18.22	12.84	12.76
3	27.91	27.85	22.31	22.25
4	39.34	39.28	34.1	33.91
5	52.19	52.10	47.36	47.30
6	66.19	66.05	68.31	68.26
7	81.91	81.84	86.56	86.49
8	97.62	97.57	95.78	95.72

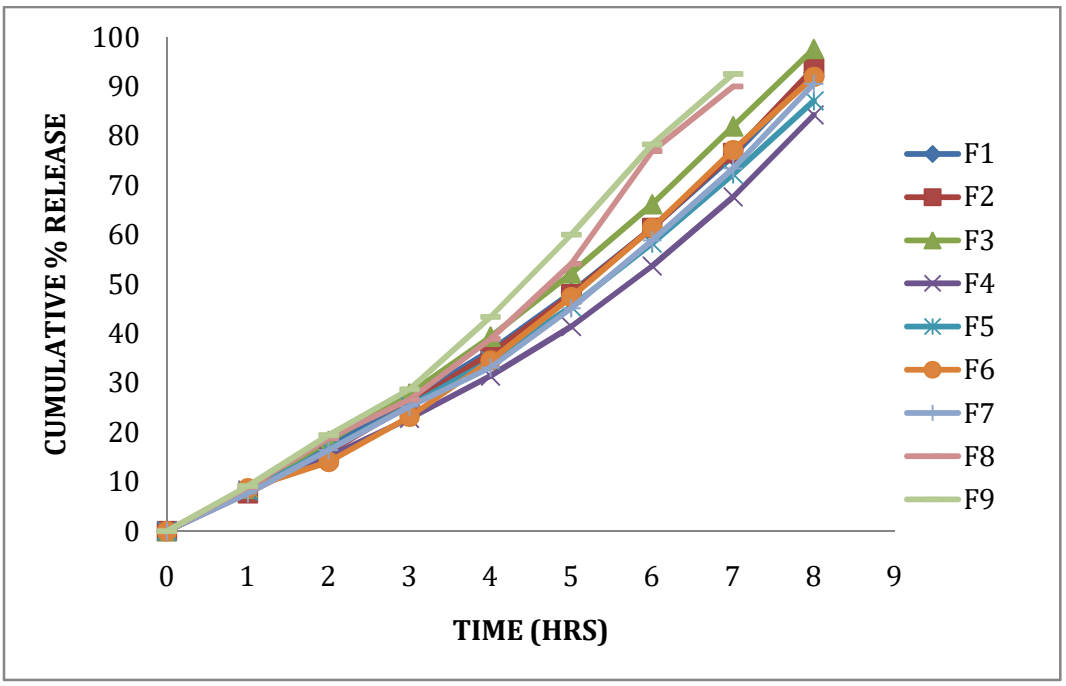

Figure 1: *In-Vitro* Dissolution of Esomeprazole Magnesium Trihydrat

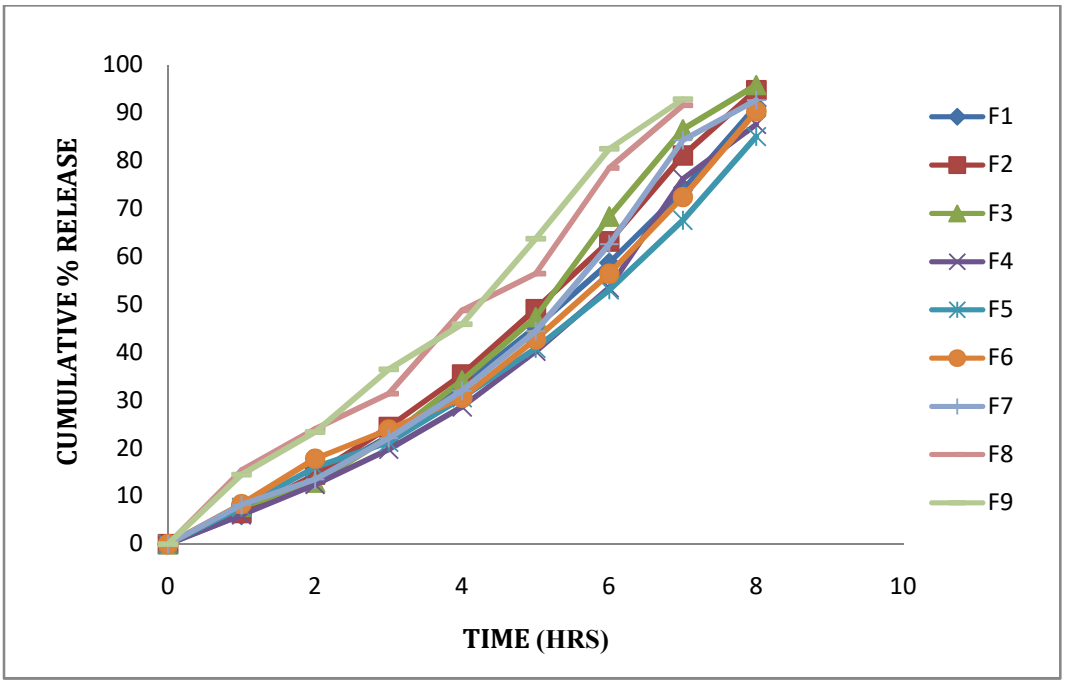

Figure 2: *In-Vitro* Dissolution of Metoclopramide Hydrochloride

No significant changes in the optimized formulation F3 of combinational buccal patch containing Esomeprazole Magnesium Trihydrate and Metoclopramide Hydrochloride in physical appearance, folding endurance, drug content and *in-vitro* drug release at storage condition of 40°C ± 2°C / 75 ± 5% RH after the end of 0 and 30 days.

Physical compatibility study shows that the drug and Excipients are physically compatible with each other.

Purity of the Esomeprazole Magnesium Trihydrate and Metoclopramide Hydrochloride was confirmed by Melting point by using capillary tube method.

Chemical compatibility study was performed using FT-IR spectroscopy and FT-IR studies revealed that there was no change in the major peaks, thus conforming no interaction between the drug and Excipient.

All formulations were prepared and evaluated for *in-vitro* drug release, physical appearance,

thickness, uniformity of weight, surface pH, folding endurance, moisture uptake study, moisture loss test, drug content , drug release kinetics, percentage elongation test.

From the *in-vitro* drug release study, it was revealed that the formulations, combinational buccal patches containing Esomeprazole Magnesium Trihydrate and Metoclopramide Hydrochloride formulated with HPMC E 15 in combine with PVP and plasticizer propylene glycol F3 showed drug release of 97.62% and 95.78% at the end of 8 hours with drug content of 99.95% and 99.4% respectively.

The formulation F3 had good folding endurance (294 folds) and water uptake capacity (4.28%) when compared to other formulations.

Formulated combinational buccal patches (F1-F9) have similar range of thickness, surface pH and good elasticity.

CONCLUSION

The present work was aimed to formulate and evaluate Esomeprazole Magnesium Trihydrate and Metoclopramide Hydrochloride combinational buccal patches using different polymers like HPMC E15, HPC, PVA in combination with PVP. The *in-vitro* release kinetics study of the optimized formulation F3 was found to be zero order and non- fickian diffusion mechanism. No changes has been observed in the physical appearance, folding endurance, drug content and *in-vitro* drug release after the end of 30 days at the storage condition of 40°C ± 2°C / 75 ± 5% RH.

REFERENCE

[1] Donald L. Wise, Hand book of Pharmaceutical controlled release technology, Pg.no. 431-433.

[2] Yie. W.Chien, Novel drug delivery system, second edition, revised and expanded, 1982. Pg.no. 197-228.

[3] Vyash and khar, Control and novel drug delivery, Pg.no. 351-358.

[4] Y.Madhusudan rao, A.V. Jithan. Advances in Drug delivery, Volume-1, Pg.no. 139-198.

[5] Gite shital Sridhar. Mucoadhesive buccal drug delivery system. An overview. Volume-3, issue -4, 2013, *JAPER.* Pg. no.319-336.

[6] N.G.Raghavendra rao. overview on buccal drug delivery systems. Volume-5, issue-4, 2013. *JPS&R*. Pg no.80-88

[7] Muhammed umar javaid. Buccal patches- An advanced route of drug dosage delivery- a review. *IJPPR*, Volume-10, Issue-3, 2017. Pg no.206-216.

[8] Nilkumar patel, Prabhakara prabhu. Design and evaluation of buccal patch containing combination of Hydrochlorthiazide and Lisinopril. *Journal of Pharmaceutical Sciences*. Volume-5, Issue-4, 2015. Pg no.143-154.

[9] Ash tosh road, Prabhakara prabhu. Design and evaluation of buccal patches containing combination of Hydrochlorthiazide and Atenolol. *IJAP*, Volume-10, Issue-2, 2018. Pg no.105-112.

[10] Radha madhavi.B. Buccal film drug delivery system- An innovative and emerging technology. *JMPOPR*. 2013.

[11] Tangri. P, satheesh madhav. Recent advances in oral mucoadhesive drug delivery systems. *IJPRD*, 2011, Volume-3, Issue-2, Pg no.151-161.

[12] Parmer HG, Jain JJ, Patel TK. Buccal patch, a technical note. *International Journal of Pharmaceutical Sciences*. Volume-4, Issue-3, 2010, Pg no.178-182.

[13] Andrews GP, Laverty TP, Jones SD. Mucoadhesive polymeric platforms for controlled drug delivery. *EJPB*. 2009, Volume-71, Issue-3, Pg no.505-518.

[14] Skulason S, Asgeirsdottir MS, Magnusson JP, Kristmundsdottir T. Evaluation of Polymeric Films for Buccal Drug Delivery. *Pharmazie.* 2009. Volume-64, issue-3. Page no.197-201.

[15] Li C, Bhatt PP, Johnston TP. *In- vitro* release and permeation of Oxytocin from a mucoadhesive buccal patch. *Pharm Dev Technol*. 1996. Volume-14, issue-1. Page no.357-364.

[16] Perioli L, Ambrogi V, Rubini D, Giovagnoli S, Ricci M, Blasi P. Novel mucoadhesive buccal formulation containing Metronidazole for the treatment of Periodontal disease. *Journal of Control Release*. 2004. Volume-95, issue-3. Page no.521-533.

[17] Smart JD. Drug delivery using buccal adhesive systems. Advanced drug delivery, A review. 1993, Volume-11, Issue-3, Pg no. 253-270.

[18] Shaojaei AH. Buccal mucosa as a route for systemic drug delivery. A review. *Journal of Pharmaceutical Sciences*.1998, Issue-1, Pg no.15-30.