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Formulation and *In Vitro/In Vivo* Evaluation of Metoclopramide Mucoadhesive Buccal Patches for Effective Pain Management

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ABSTRACT

The report planned to design plus valuate mucoadhesive buccal patches of Metoclopramide for orthopedic treatment of pain and inflammations. All eight formulation acquire numerous evaluation parameters, it used to be complete for which F1 confirmed good mucoadhesive strength, encouraging pressurized and arrant drug release, easiest *In-vivo* residence time, swelling index and pH shows the best formulation. The acquired *in vivo* effects show that the put concentration of Metoclopramide in the mouth cavity was retained above 5 pg/mE for 130 min. The effect stands for so the buccal patches of metoclopramide could be a good choice to avoid the unsatisfactory systemic unwanted effects and will be planned as a new therapeutic tool around against orthopedic diseases and disturbances.

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INTRODUCTION

Buccal drug delivery provides an attractive strategy to the oral route of drug administration, particularly in overcoming deficiencies associated with oral administration. It has excellent accessibility, an expanse of smooth muscle, and relatively immobile mucosa, hence suitable for administration of retentive dosage forms which are associated with severe pain and discomfort [1].

The various mucoadhesive formulations were suggested for buccal delivery that includes; patches, tablets, and gels.

Buccal patches overcome some of the drawbacks of other dosage forms; as they have unique characteristics including flexibility and relatively rapid onset of drug delivery. Moreover, since mucoadhesion implies attachment to the buccal mucosa for an extended period [2].

The present study was conducted to explore the feasibility and effectiveness of buccal mucoadhesive drug delivery of metoclopramide as an effective alternative in relieving pain after surgery or orthopedic injury.

In an attempt to reduce the relatively high incidence of serious adverse effects associated with the systemic use, a growing number of topical formulations of these drugs have become commercially available [3].

MATERIALS AND METHODS

Metoclopramide purchased free of charge sample from B.M.R Chemicals, Hyderabad, Hydroxypropylmethylcellulose E4M, Eudragit RLP, ethylcellulose 20 Premium, Polyvinylpyrrolidone, Hydroxypropyl cellulose to be a present sample of Hi-media laboratory. All other chemical compounds victimized were of analytic grade.

Methodology

Patches have been planned out by solvent casting technique. For all formulae, the calculated amount of Metoclopramide (1 % w/v) was dissolved in the solvent system used, either (1:1) dichloromethane/ethanol 96 % mixture or ethanol 96 % alone, after levigation with the proposed amount of plasticizer system (Tween 80), then the calculated amount of polymer was incorporated into the drug solution under continuous stirring using a magnetic stirrer and was left overnight to make certain a visible bubble-free solution.

For the deliberate on the part of Polymers (HPMC E4M, Eudragit RLPO, EC, PVP, HPC) used to be dissolved in the production capacity of 1 % glacial acetic acid and left overnight to ensure a clear solution, then the calculated amount of Metoclopramide was levigated with the plasticizer mixture (Tween 80) and propylene glycol (as solubilizing agent) and dissolved in ethanol 96 % and the drug solution was finally incorporated to the polymer solution under continuous stirring [Table 1].

The solutions were cast into glass Petri dishes of 5.5 cm diameter and were allowed to dry overnight in the oven at 40°C, dried film used to be small pieces patches, packed in wax paper, plus keep in a desiccator [4].

Compatibility Studies

Differential Scanning Calorimetry

DSC (DSC-60, Shimadzu, Japan) was once to written report spectacular thermic behavior of the planned out patches and any workable interactions between the drug and abundant patch components [5].

Evaluation of Metoclopramide Mucoadhesive Patches

Viscosity

It is determined by Brookfield digital viscometer used to be utilized all the formulations [6].

Thickness

The thickness of patches of each type of formulation was measured using an electronic digital caliper respectively [7].

pH

It was sounded by striking pH wrapping paper outwardly of your puffed patch [8].

Drug Content

This was determined by dissolving the medicated patch (1×3 cm) containing 10 mg Metoclopramide in 100 ml phosphate buffer pH 6.8 under occasional shaking overnight. Then an aliquot was filtered through a 0.45 μm membrane filter [9].

Swelling Index

The mesh containing the patch sample was then submerged into 15 mL of phosphate buffer at pH 6.8. A definite time intervals (5, 15, 30, 45 and 60 min), the basket was removed, dried carefully using absorbent tissue, and reweighed [10].

% Swelling Index = (Wt - W0)/Wt × 100

Tensile Strength

Mechanical properties of the prepared patches were evaluated using Instron universal testing instrument (model 8500 digital control, Instron) with a 1 kg load cell. A patch with dimensions of (1 × 3 cm) was held between two clamps positioned at a distance of 1 cm. During measurement, the patch was pulled by the top clamp at a rate of 100 mm/m; the force and elongation were measured when the patch broke [11]. Measurements were run in triplicate for each patch. Tensile strength (TS) is the maximum stress applied to a point at which the patch specimen breaks and can be computed from the following equation.

TS (MPa) = breaking force (N)/cross-sectional area (mm^2)

Bioadhesive Strength

The bioadhesive strength of different patches was measured using locally assembled apparatus and rabbit buccal mucosa as a model mucosal membrane [12]. The surface of the mucosal membrane was moistened with 25 μL phosphate buffer at pH 6.8. The two holders were put in contact with each other with light pressure between fingers for 1 min (preload time) to facilitate adhesion bonding. The upper tissue holder was allowed to hang on an iron stand with the help of an aluminum wire fastened with a hook provided on the back of the holder.

Force of adhesion (N) = (bioadhesive strength (g) x 9.81)/1000 bond strength (N m-2) = force of adhesion/patch surface area

In-vitro Drug Release

The dissolution using USP type II paddle apparatus in 6.8 PH phosphate buffer (900 ml) at $37^0C \pm 0.5^0C$

Table 1: Composition of Various Formulations of Metoclopramide Buccal Patches

Formulations	Metoclopramide	HPMC E4M	Eudragit RLPO	EC (20P)	PVP	HPC (%)	Tween 80 (%)	PG (%)	Ethanol DCM (1:1) (ml)	Ethanol 96 (ml)	1 % glacial acetic Acid (ml)
F1 (mg)	900	900	500	-	-	3	1		100	-	-
F2 (mg)	900	900	-	-	-	3	1		100	-	-
F3 (mg)	900	-	500	500	-	3	1		-	100	-
F4 (mg)	900	-	500	-	-	3	0.5	4	-	100	-
F5 (mg)	900	500	-	500	-	3	0.5		-	30	70
F6 (mg)	900	-	-	500	-	3	0.5		-	30	70
F7 (mg)	900	-	500	-	500	3	1.5		100	-	-
F8 (mg)	900	-	-	-	500	3	1.5		100	-	-

Table 2: Mechanical Properties and Bioadhesive Parameters of Different Metoclopromide Buccal Patches

Formulation code	Tensile Strength (MPa)	Viscosity (cps)	Bioadhesive Strength (g)	pH	Drug Content (%)	Thickness (mm)
F1	8.20 ± 0.10	262.3 ± 1.35	37.45 ± 0.43	6.5	96.2 ± 0.24	0.16 ± 0.01
F2	7.28 ± 0.04	286.1 ± 1.04	37.17 ± 0.66	6.2	76.5 ± 0.25	0.17 ± 0.13
F3	7.16 ± 0.15	375.7 ± 1.15	22.77 ± 2.40	6.1	66.7 ± 0.14	0.19 ± 0.15
F4	5.56 ± 0.15	109.5 ± 1.23	25.26 ± 0.64	6.3	76.1 ± 0.17	0.21 ± 0.17
F5	7.20 ± 0.10	167.2 ± 1.01	35.69 ± 2.32	6.1	66.5 ± 0.14	0.23 ± 0.19
F6	10.36 ± 0.16	874.7 ± 1.62	26.32 ± 0.22	6.0	86.2 ± 0.16	0.26 ± 0.21
F7	7.09 ± 0.73	235.1 ± 1.31	44.59 ± 2.84	6.4	79.8 ± 0.15	0.18 ± 0.12
F8	6.06 ± 0.22	101.1 ± 1.03	25.49 ± 0.23	6.3	86.7 ± 0.18	0.22 ± 0.14

Table 3: % Swelling Index of Different Metoclopramide Buccal Patches

Time (min)	% Swelling Index of Formulations							
	F1	F2	F3	F4	F5	F6	F7	F8
5	92.2 ± 1.7	89.5 ± 1.2	87.1 ± 1.3	88.3 ± 1.7	87.6 ± 1.3	89.3 ± 1.3	93.6 ± 1.4	98.2 ± 1.4
10	88.2 ± 1.4	88.8 ± 1.4	86.5 ± 1.6	84.8 ± 1.4	83.5 ± 1.4	84.2 ± 1.6	91.5 ± 1.7	97.1 ± 1.7
15	82.2 ± 1.6	87.5 ± 1.4	85.4 ± 1.5	82.6 ± 1.5	81.2 ± 1.2	79.9 ± 1.4	89.3 ± 1.4	95.7 ± 1.4
20	79.6 ± 1.7	86.7 ± 1.5	84.7 ± 1.6	81.4 ± 1.7	80.6 ± 1.5	76.3 ± 1.3	88.6 ± 1.5	94.6 ± 1.8
25	77.3 ± 1.9	84.3 ± 1.4	83.4 ± 1.8	80.3 ± 1.5	79.5 ± 1.1	68.3 ± 1.4	86.5 ± 1.2	93.1 ± 1.8
30	74.1 ± 1.8	82.5 ± 1.7	81.4 ± 1.7	78.4 ± 1.2	76.7 ± 1.6	66.5 ± 1.7	83.9 ± 1.8	91.5 ± 1.7
35	72.6 ± 1.6	81.2 ± 1.3	80.6 ± 1.4	75.6 ± 1.4	73.6 ± 1.5	64.1 ± 1.8	82.3 ± 1.5	89.3 ± 1.6
40	69.2 ± 1.4	80.4 ± 1.7	78.8 ± 1.5	73.8 ± 1.6	72.6 ± 1.8	58.6 ± 1.3	80.6 ± 1.8	87.6 ± 1.2
45	66.4 ± 1.5	79.9 ± 1.8	77.3 ± 1.2	71.9 ± 1.7	70.4 ± 1.9	51.4 ± 1.6	79.5 ± 1.7	87.1 ± 1.8
50	62.3± 1.8	78.5 ± 1.9	75.6 ± 1.3	70.3 ± 1.5	67.4 ± 1.5	50.7 ± 1.7	76.8 ± 1.9	86.4 ± 1.7
55	50.2 ± 1.5	77.8 ± 1.3	74.1 ± 1.7	66.7 ± 1.4	59.6 ± 1.8	48.3 ± 1.6	74.7 ± 1.6	84.8 ± 1.7
60	53.7 ± 1.4	75.8 ± 1.3	72.8 ± 1.5	59.8 ± 1.2	56.7 ± 1.5	46.2 ± 1.5	71.3 ± 1.3	82.6 ± 1.5

Table 4: Cumulative Drug Release of Metoclopramide Mucoadhesive Buccal Patches

Time	% Cumulative drug release							
(hrs)	F1	F2	F3	F4	F5	F6	F7	F8
1	15.1 ±1.2	11.2±1.31	12.8±2.01	11.6±1.11	16.2±1.32	11.3±1.10	10.2±1.23	19.30±1.21
2	33.6±2.54	35.8±1.84	26.0±1.34	31.6±1.32	36.0±1.21	38.9±1.33	26.1±1.12	26.4±2.11
3	49.8±2.43	48.6±2.21	49.8±1.34	48.8±1.61	51.4±1.45	56.2±2.34	43.2±1.32	44.2±3.12
4	58.8±1.34	64.2±2.24	64.8±1.21	61.4±2.23	74.0±1.21	71.3±1.12	61.4±1.24	69.6±2.13
5	81.0±3.24	87.8±3.33	88.6±1.33	84.0±1.34	83.0±1.12	80.1±1.28	89.6±1.33	86.4±2.34
6	98.1±1.11	95.1±0.21	94.6±1.18	93.0±2.32	90.2±1.56	93.2±1.12	96.4±0.11	91.2±4.32

at speed 50±5 rpm. At specified time intervals, 5 ml samples were collected and immediately replaced with an equal volume of fresh medium. Samples were suitably diluted and analyzed by using UV spectrophotometer λmax 271 nm and cumulative % drug released was calculated. The *in vitro* release data were fitted into zero-order, first-order, Higuchi, and Korsmeyer-Peppas models [13].

In-vivo Residence Time

The adhesion capacity of Metoclopramide mucoadhesive patches was tested in five healthy rabbits. One patch adhered to the buccal mucosa of each volunteer [14]. The residence time, strength of adhesion, bitterness, and fragmentation of the patch were recorded. Animal Ethics committee approval no. 1688/PO/E/2020/CPCSEA, Sanztme Ltd Healthcare Business, Hyderabad.

In vivo Evaluation of the Selected Metoclopramide Patch

Analysis of Saliva Samples

One hundred microliters of saliva samples were transferred to centrifuge tubes and 200 μL of acetonitrile was added to precipitate any soluble proteins. The tubes were vortex mixed for 10 s and cen-

Table 5: The Kinetic Parameters of Metoclopramide Release Data According to Different Kinetic Models

Formula Code	Zero-order	First order	Higuchi	Krosmeyer Peppas	
	r^2	r^2	r^2	r^2	n
F1	0.855	0.825	0.938	0.851	0.514
F2	0.884	0.751	0.867	0.856	0.488
F3	0.738	0.633	0.953	0.818	0.332
F4	0.747	0.674	0.853	0.968	0.447
F5	0.815	0.725	0.967	0.835	0.355
F6	0.776	0.638	0.866	0.875	0.481
F7	0.857	0.753	0.834	0.887	0.183
F8	0.836	0.835	0.745	0.824	0.378

Table 6: Pharmacokinetic parameters of metoclopramide released in saliva after application of the selected patch F1 (HPMC/Eudragit) to the buccal mucosa of rabbit

SI.No	AUC $^{0-180}$	C_{max}	T (min)
1	1682.3	7.715	110
2	1387.4	39.11	40
3	1472.8	17.88	80
4	1774.7	38.81	40
5	1316.5	21.43	50
6	1673.8	25.32	50
7	657.3	14.84	40

trifuged at 10000 rpm for 30 min at 40°C. Twenty microliters of the supernatant were then injected into the chromatographic system and analyzed for drug content with HPLC. From the measured salivary concentration, the following parameters [15] were calculated Cmax, Tmax, and AUC_{0-180}.

RESULTS AND DISCUSSION

Differential Scanning Calorimetry

Thermograms recorded for pure polymer & Drug was similar, showing no thermal events [Figure 1 and Figure 2]. For the metoclopramide displayed to a pointy endothermic peak at 131.83^{0}C similar to the melting of the overall drug having a heat of fusion (ΔH) of -803.95 mJ. For the drug & polymers displayed to a pointy endothermic peak at 152.60^{0}C & heat of fusion (ΔH) of -518.71 mJ.

Viscosity

The viscosity of different polymer solutions was measured and the results were ranges from 101.1 $\pm$ 1.03 cps 874.7 $\pm$ 1.62 cps [Table 2].

Thickness

Thickness in the range of 0.16 $\pm$ 0.01mm and 0.26 $\pm$ 0.21 mm of all patch tests were uniform inside each formulation [Table 2].

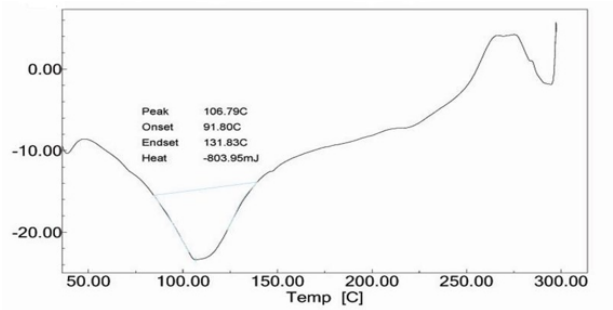

Figure 1: DSC Thermogram of Pure Metoclopramide

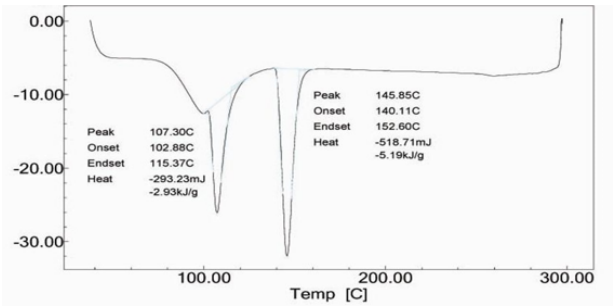

Figure 2: DSC Thermogram of Drug and Polymers

pH

The sort out formulations supplied a suitable pH range of 6-6.5 that's compatible along with buccal mucosa [Table 2].

Drug Content

The common percent of drug content consistening [Table 2] of various patches ranged from 66.5 ± 0.14 % and 96.2 ± 0.24 %.

Swelling Index

The patches have been ranges from 50.2 ± 1.5 % and 96.2 ± 1.7 %. On the other hand, a slight decrease in the swelling was observed upon the incorporation of water insoluble polymers like Eudragit which are not hydrophilic and therefore absorb water in smaller amounts than hydrophilic polymers, which lead to less swelling upon hydration [Table 3].

Tensile Strength

It is observed from the results that all formulations provide good mechanical properties (hard and tough) have been ranges from 6.06 ± 0.22 MPa to 10.36 ± 0.16 MPa.

Bioadhesive Strength

The entire formulations [Table 2] follow the variety of 22.77 ± 2.40g to 44.59 ± 2.84 g.

In vitro Drug Release Study

These release studies unconcealed so the order of waiver as proven in Table 4 and Figure 3. The kinetic analysis of the *in vitro* release data of metoclopramide from buccoadhesive patches [Table 5].

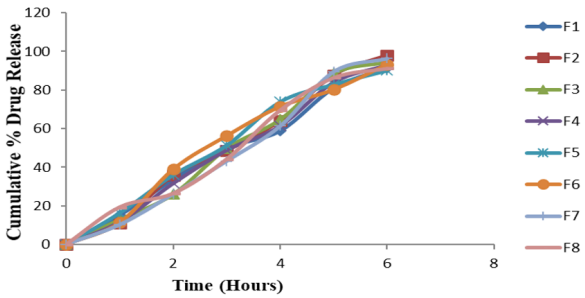

Figure 3: Cumulative % Drug Release of Metoclopramide Mucoadhesive Buccal Patches

In vivo Residence Time

The results demonstrated the superiority of F1 (HPMC/ Eudragit) to stay at the buccal mucous membrane the rabbit.

In vivo Evaluation of the Selected Patch

In vivo evaluation of the selected patch F1 on rabbit revealed that the patch did not cause discomfort to the rabbit, no severe salivation or mouth drying and no irritation was observed. The patch was placed in the region of the upper canine between the cheek and gingiva for 3 h and food and drink were restricted throughout the experiment. Inter individual variations were observed for AUC_{0-180}, Cmax, and Tmax. This was probably due to the variation between individuals concerning the salivary flow rate, which influences patch hydration and the release of drugs in the mouth [Table 6].

CONCLUSION

The present study concludes that these erodible mucoadhesive buccal patches containing metoclopramide might be very auspicious for utile doses to with the systemic currency in suffers as well as orthopedic accidents. Based on the evaluation of the results, it was concluded that F1 showed good mucoadhesive strength, *In vivo* residence time, swelling index and pH shows the excellent results. Accordingly F1 could be selected as the best formula among the formulations studied and was subject to further *in vivo* study. Buccal patches exhibited controlled release over more than 8 h with no irritation on the mucosa. Thus these patches can be selected for the development of buccal patches for effective therapeutic uses.

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Conflict of Interest

The authors attest that they have no conflict of interest in this study.

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