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FORMULATION AND COMPARATIVE EVALUATION OF PANTOPRAZOLE BUCCAL PATCHES USING NATURAL AND SYNTHETIC POLYMER

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Abstract:

Gastro-oesophageal reflux disease is a chronic condition of mucosal damage. GERD is caused by the regurgitation of stomach acid into the esophagus. Pantoprazole is a proton pump inhibitor which acts against GERD. This proposed work is to formulate and evaluate pantoprazole buccal patches using synthetic (HPMC K100) and natural (sodium alginate) film forming polymers. Solvent casting method was used for the preparation of patches. Polyethylene glycol and glycerol were used as plasticizers. Pantoprazole is a highly potent proton pump inhibitor used in treatment of erosion and ulceration of the esophagus caused by gastro esophageal reflux disease and it acts systemically. Preformulation studies were performed. FT-IR analysis showed the drug and polymers were compatible. Six formulations were prepared, F1, F2 and F3 using different concentration of sodium alginate. F4, F5 and F6 were formulated using different concentrations of HPMC k100. In vitro dissolution studies were done. It was seen that the formulation F4 showed maximum drug release (97.42%). Surface pH of the formulated patches was found to be around 7. Folding endurance, disintegration and dissolving time, moisture content, swelling index also were performed and all the tests showed a satisfactory results. From all the evaluation parameters, F4 formulation was found to be better showing sustained release when compared to other formulations. The kinetic study of F4 formulation was done and it was found that the formulation follows zero order.

Key words: *Pantoprazole; HPMC K100; Sodium alginate; FT-IR; GERD.*

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INTRODUCTION:

The buccal patch carries a drug reservoir layer from which the drug is discharged in a controlled manner, and a bioadhesive surface for attachment to mucosal membrane. Additionally it may contain a backing membrane. Films/patches were made by either solvent casting or hot melt extrusion technique. They deliver a measured dose of drug to the site and it is the advantage over creams and ointments [1].

Pantoprazole is used for short-term treatment of erosion and ulceration of the esophagus for adults and pediatric patients with 5 years of age and older caused by gastro-esophageal reflux disease. It can be used as a maintenance therapy for long-term use after initial response is obtained, but there have not been any controlled studies about the use of pantoprazole past duration of 12 months. Pantoprazole may also be used in combination with antibiotics to treat ulcers caused by Helicobacter pylori. It can also be used for long term treatment of Zollinger-Ellison syndrome [2]. The mechanism of action of pantoprazole is to inhibit the final step in gastric acid production.

Buccal patches deliver the drugs directly into systemic circulation through mucus membrane thereby bypassing the first pass effect. Contact with digestive juice of gastrointestinal tract is avoided which might be unsuitable for stability of many drugs. This is painless and without discomfort, precise dosage form and facilitates ease of removal without significant associated pain. Moreover it shows better stability, patient compliance, uniform and sustained drug release and above all easy and cheap methods of preparation which can be done with various commonly available biocompatible polymers [3].

MATERIALS AND METHODS:

Pantoprazole, HPMC K100M and polyethylene glycol Yarrow chem. Products, Mumbai, polyvinyl alcohol from Loba chem pvt ltd and sodium alginate from Thomas baker(chemical)ltd,Mumbai. All other ingredients used were of analytical grade.

METHODOLOGY

Preparation of Calibration Curve:

The stock solution was prepared by accurately weighing 100 mg of pantoprazole Sodium and dissolved in 10 ml of phosphate buffer (6.8 pH) in volumetric flask. From the stock solution 0.1, 0.5, 1, 1.5, 2.0, 2.5 ml was pipetted out and made up to 10ml with phosphate buffer (6.8pH) to prepare the concentrations in µg/mL. The prepared concentrations were analyzed at 295 nm by spectrophotometer. Absorbance mean of five determinations was taken to check the reproducibility. The observed absorbance was subjected to regression analysis, to study the linearity and other optical characteristics [4].

Drug –Excipient Compatibility Study

The identification of pure drug and drug-excipient compatibility study was done by KBr pellet technique using Shimanduz, Japan IR Affinity - 1. The standard spectrum was correlated with the reference IR spectra. The spectra were scanned over the range of 4000-400cm^{-1} with a resolution of 4 cm^{-1}. These spectra were compared and interpreted for shifting of major functional peaks and disappearance or appearance of new functional peaks [6].

Preparation of Buccal Patches

Preparation of Backing Membrane

A 4% (w/v) solution of polyvinyl alcohol (PVA) in distilled water was prepared by using mechanical stirrer. 2ml of the solution was poured in the square mould on the glass plate. The rate of evaporation of solvent was controlled by inverting a glass funnel on the mould and was allowed to dry at 40^0 C ± 2^0 C for a period of 4 hrs in hot air oven. After 4 hrs mould was removed and air dried for 24 hrs [7].

Fabrication of Pantoprazole Buccal Patches

Buccal patches were prepared by solvent casting technique. Glass moulds were used for casting of patches. Formulations were designed as shown in the table No:1, in which HPMC k100 was taken as the synthetic polymer and sodium alginate as the natural polymer. The water soluble ingredients such as HPMC and sodium alginate are dissolved to form a clear viscous solution and the drug along with other excipients is dissolved in suitable solvent which is water itself, then both the solutions are mixed and stirred and finally casted in to the Petri plate and dried. Both the solutions are mixed resulting solution is cast as a film and allowed to dry, film is collected**.** After complete evaporation of solvent, cast films were obtained, which were then cut into pieces, wrapped in an aluminum foil and stored in a desiccator at room temperature in a dark place for further evaluation studies [8].

Table 1: Formulation of pantoprazole buccal patches

Formulation	Pantoprazole (mg)	Sodium Alginate (mg)	HPMC K100(mg)	PEG (ml)	Glycerine (ml)	Distilled water (ml)
F_1	**100**	**200**	**-**	**0.4**	**0.2**	**10**
F_2	**100**	**250**	**-**	**0.4**	**0.2**	**10**
F_3	**100**	**300**	**-**	**0.4**	**0.2**	**10**
F_4	**100**	**-**	**200**	**0.4**	**0.2**	**10**
F_5	**100**	**-**	**250**	**0.4**	**0.2**	**10**
F_6	**100**	**-**	**300**	**0.4**	**0.2**	**10**

Characterization of Buccal Patches

Physical Appearance

All the prepared patches were visually inspected for color, clarity, flexibility and smoothness [9].

Thickness

The thickness of each film was measured by screw gauze. The thickness was measured at three different places on each film and the average thickness of the film was taken as the thickness of the film [10].

Weight uniformity

The patches were dried at 60°C before weighing. The weight uniformity of the patches are measured by cutting and weighing 1 cm^2 piece of 3 patches and then calculating the weight variation. The mean of the 3 is taken as the weight of the patch. The individual weight should not deviate significantly from average weight [11].

Folding Endurance

The folding endurance was measured manually for the prepared films. A strip of film 1cm^2 was cut and repeatedly folded at the same place till it broken. The number of times the film could be folded at the same place without breaking or cracking gives the value of folding endurance [12].

Percentage moisture content

Individually weighed patches were kept in the desiccators containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the patches are to be reweighed and percentage of moisture content was calculated by the formula [13,14].

$$\text{Percentage moisture content} = \frac{(\text{Initial weight} - \text{Final weight}) \times 100}{\text{Initial weight}}$$

Dissolving time

The dissolving time was determined by placing the patches in a beaker containing 50ml of phosphate buffer (pH 6.8). Time required by the patche to dissolve completely was noted [15].

Disintegration time

Test was performed using disintegration test apparatus. 5cm^2 film was placed in the basket, raised and lowered it in such a manner that the complete up and down movement at a rate to achieve equivalent to thirty times a minute. Time required by the film to achieve no trace of film remaining above the gauze was noted [15].

Swelling Index

A drug-loaded patch of 1x1 cm2 was weighed on a pre-weighed cover slip. It was kept in a petridish and 50 ml of phosphate saline buffer, pH 6.8 was added. After every five minute, the cover slip was removed and weighed up to 30 min. The difference in the weight gives the weight increase due to absorption of water and swelling of patch [16]. The swelling index, S was calculated using the following equation:

$$S = \frac{X_t - Xo}{Xo}$$

Where X_t is the weight of the swollen patch after time t and Xo is the original patch weight at zero time.

Surface pH

The film to be tested was placed in a petridish and was moistened with 0.5 ml of phosphate buffered saline, kept for 1 hour. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and kept for 1 min to allow equilibrium condition [17].

Drug content

A circular film of 2.5cm diameter was cut and placed in a beaker. 100 ml of phosphate buffered saline solution (pH 6.8) was placed. The contents were stirred in magnetic stirrer to dissolve the film. The contents were transferred to a volumetric flask (100 ml). The absorbance of the solution was measured against the corresponding blank solution at 295 nm. As the absorbance noted above 1mcg/ml, 1ml of the

stock was further diluted to 10ml of phosphate buffered saline solution (pH6.8) and absorbance was measured at 295nm [18,19].

***In-vitro* Dissolution Studies**

Dissolution apparatus USP type II rotating paddle method was used to study drug release from buccal films. The dissolution medium consisted of 400ml of phosphate saline buffer (pH 6.8). The study was performed at 37 ^{0}C with 100 rpm. One side of each buccal film (3 films) (2.5 cm diameter) was attached to glass slide with cynoacrylate glue. The glass slide was put to bottom of the vessel so that film remained on the upper side of the glass slide. Sample (5 ml) was withdrawn at predetermined time interval of 40, 80, 120, 160, 200, 240 minutes and replaced with fresh medium. The samples were filtered through whatmann filter paper and assayed by UV spectrophotometer at 295nm [20,21].

RESULTS:

Sl.No	Concentration (µg/ml)	Absorbance
1	0	0.0
2	5	0.225
3	10	0.425
4	15	0.652
5	20	0.846
6	25	1.080

Table 2: Calibration curve for Pantoprazole Sodium in Phosphate Buffer pH 6.8

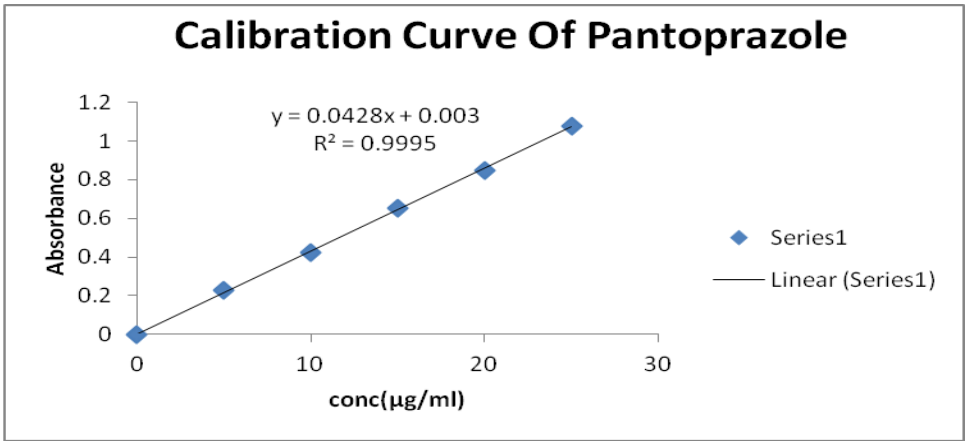

Fig. 1: Standard plot of pantoprazole in pH 6.8 phosphate buffer solution

FTIR Spectroscopy:

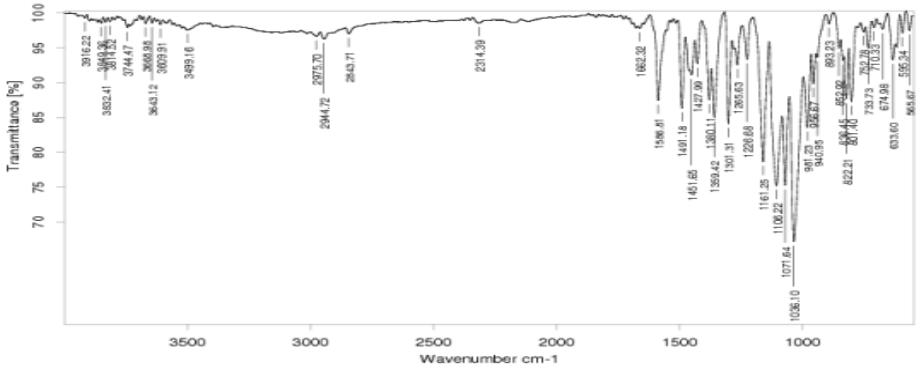

Fig. 2: FTIR Of pantoprazole

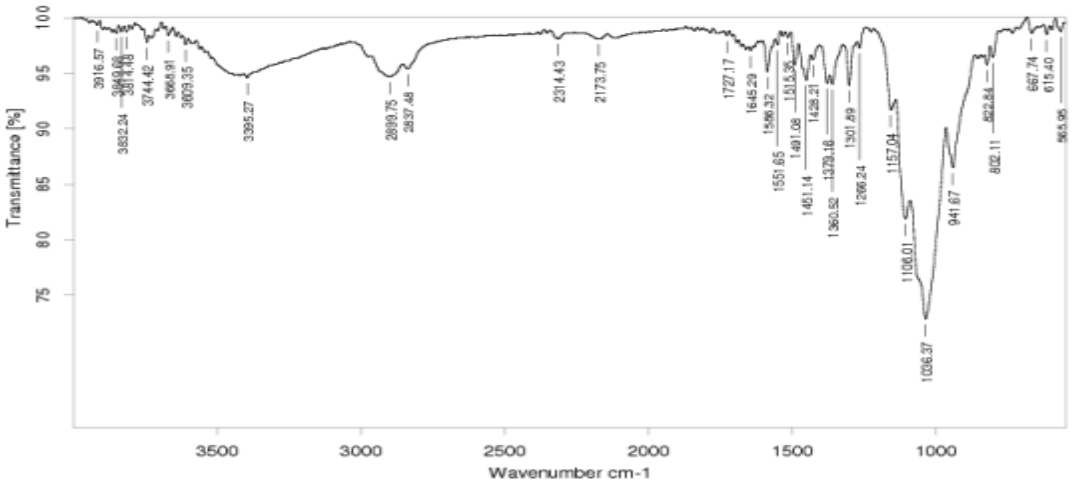

Fig. 3: FTIR of pantoprazole and HPMC

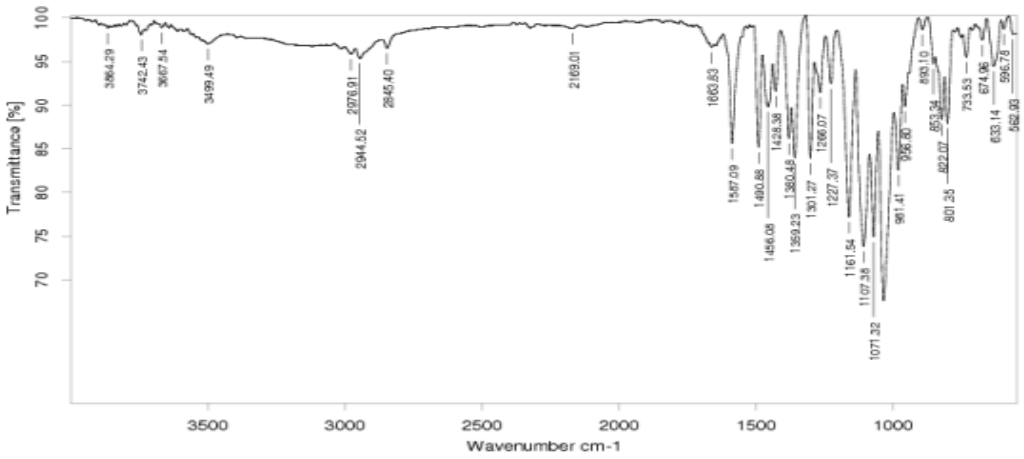

Fig. 4: FTIR of pantoprazole and Sodium Alginate

The FTIR spectroscopy studies were carried out for pure drug alone and combination of drug and polymer. IR spectrum of pantoprazole alone and their physical mixture of HPMC K100 and Sodium alginate are shown in Figures: 2, 3 and 4 respectively.

Physical appearance of buccal patches

All formulations prepared were translucent, light yellow colour with smooth surface without any grittiness and were found to be flexible in nature.

Thickness

The thickness of patches was evaluated with the use of a screw gauge and was found to be in the range of 0.045-0.094 mm.

Weight uniformity

Drug loaded buccal patches were tested for uniformity of weight and the results of weight uniformity are given above, was found to be within the limit.

Folding Endurance

In general, folding endurance of all the film was found to be satisfactory indicating good strength and elasticity. Folding endurance was found in the range 207-243.

Percentage moisture content

Percentage moisture content was found to be in the range of 1.29-1.83%.

Dissolving time

The time for the pantoprazole patches to dissolve in the buffer solution increases with increase in the concentration of polymer. The dissolving time ranges from 188 to 248 min.

Disintegration time

The disintegration time of all the formulations was determined as described in the methodology. The disintegration time ranges from 112 to 160min.

Swelling index

Swelling index of all films was calculated and it was in the range of13.13%-20.55%.

Surface pH

Surface pH of all the formulations was determined as described in the methodology chapter. All the formulations were found to have pH between 6.8 – 7.4.

Drug Content

The drug content in each buccal patch was analyzed spectrometrically and is observed that drug content value ranges from 83.14 to 86.36 %.

Table 3: Characterization of Buccal Patches

Formulation code	Thickness(mm)	Weight uniformity(gm)	Folding endurance	Swelling index	Dissolving time (min)
F1	0.0646	0.0093	207	13.13	223
F2	0.0833	0.0143	212	14.63	238
F3	0.0943	0.0167	222	15.30	248
F4	0.0450	0.0087	223	15.43	188
F5	0.0643	0.0133	232	18.57	211
F6	0.0756	0.0150	243	20.53	233

Formulation code	Percentage moisture content	Surface pH	Percentage drug content	Disintegration time (min)
F1	1.29	7.24	95.05	133
F2	1.36	7.29	94.24	143
F3	1.59	7.32	93.14	160
F4	1.43	7.36	96.36	112
F5	1.58	7.26	95.86	136
F6	1.83	7.14	94.06	150

Table 4: *In-vitro* studies

Sl.No	Time (min)	Percentage drug release (%)					
		F1	F2	F3	F4	F5	F6
1	**0**	**0**	**0**	**0**	**0**	**0**	**0**
2	**60**	**19.68**	**16.34**	**14.97**	**20.23**	**19.56**	**18.62**
3	**120**	**42.35**	**36.91**	**32.68**	**45.89**	**34.56**	**36.71**
4	**180**	**50.32**	**43.27**	**44.56**	**54.67**	**52.38**	**48.89**
5	**240**	**70.56**	**68.89**	**68.71**	**79.19**	**79.23**	**75.17**
6	**300**	**82.98**	**78.34**	**76.78**	**89.91**	**85.34**	**81.47**
7	**360**	**87.98**	**86.32**	**82.68**	**97.42**	**91.05**	**84.55**

Percentage drug release of different buccal formulations pantoprazole in patches

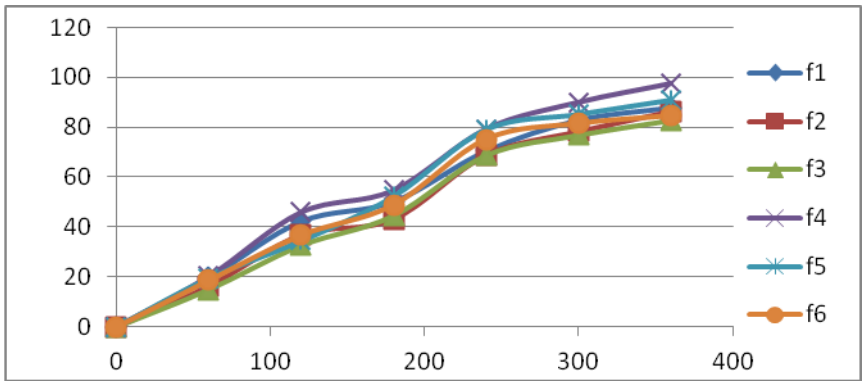

Fig.5: Percentage drug release of pantoprazole buccal patches

The cumulative percentage release from the formulation was found in the range of 82.68% - 97.42%. From the six formulations namely F4 with

HPMC K100 shows satisfactory sustained effect and a maximum release of about 97.42% in 6 hrs.

CONCLUSION:

Pantoprazole sodium, a proton pump inhibitor was selected for the preparation of buccal delivery system as it complies the physicochemical properties required for permeation through mucous membrane. FTIR studies showed that the drug was compatible with the added polymers. PEG600 acts as co solvent for inducing solubility of drug and also as plasticizer.

The patches were prepared by solvent evaporation method. The patches were subjected for following evaluation parameters such as physical appearance, weight variation, thickness, folding endurance, drug content, percentage moisture content, swelling index, surface pH and *In-vitro* studies. The results of the evaluation parameters were within the limit.

Six different patches marked as F1, F2, F3, F4, F5 and F6 were formulated by changing the concentration of polymers. All the formulation have the drug content in the range of 93.14-96.36w/w. The in-vitro release studies were conducted and more than 80% could be released in 340min. It was found that thickness of patches increases with increase in concentration of the polymer. The percentage drug release was found to more in the formulation F4 in which HPMC K100 (Synthetic polymer) were used as the polymer.

From the present investigation, it can be concluded that such Mucoadhesive buccal films of pantoprazole may provide buccal delivery for prolonged periods in the management of gastro esophageal reflux disease, which can be a good way to bypass the extensive hepatic first pass metabolism.

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