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FORMULATION AND EVALUATION OF PANTOPRAZOLE BUCCAL PATCHES BY SOLVENT CASTING METHODS USING DIFFERENT POLYMERS

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ABSTRACT
Buccal delivery of the desired drug using mucoadhesive polymers has been the subject of interest since the early 1980s Advantages associated with buccal drug delivery have rendered this route of administration useful for a variety of drugs. The goal of the present investigation was to design and evaluate mucoadhesive buccal patches of pantoprazole which offers on attractive route of administration for systemic drug delivery. Pantoprazole (dose, 10-40mg) is proton pump inhibitor used in treatment of erosion and ulceration of the esophagus caused by gastro esophageal reflux disease Its oral bioavailability is 77% metabolized in the liver by cyp-450 system . The patches were prepared and evaluated for their thickness uniformity, folding endurance, weight uniformity, content uniformity, and is vitro release studies were conducted for pantoprazole loaded patches in phosphate buffer (pH 7.4) solution.

KEYWORDS: Pantoprazole, HPMC, PVP, P G.

INTRODUCTION
Extensive research efforts have recently been focused on placing a drug delivery system in a particular region of the body for maximizing biological drug availability and minimizing dose-dependent side effects. Buccal delivery of drugs provides an attractive alternate to other conventional methods of systemic drug administration, since buccal mucosa is relatively permeable with rich blood supply and acts as an excellent site for the absorption of drugs. The administration of drugs via buccal route facilitates a direct entry of drug molecules into the systemic circulation, avoiding the first-pass metabolism and drug degradation in the harsh gastrointestinal environment, which are often associated with oral administration 3-5. The buccal cavity is easily accessible for self medication. Hence it is safe and well accepted by patients, since buccal patches can be very easily administered and even removed from the application site, terminating the input of drug whenever desired. Moreover, buccal patches provide more flexibility than other drug deliveries.

Pantoprazole (dose, 10-40mg) is proton pump inhibitor used in treatment of erosion and ulceration of the esophagus caused by gastro esophageal reflux disease. Its oral bioavailability is 77% metabolized in the liver by cyp-450 system. During last few decades, mucoadhesive polymers received considerable attention as platforms for buccal delivery of drugs due to their ability to localize the dosage form in the specific regions to enhance drug bioavailability".

Permeation Enhancers have demonstrated their effectiveness in delivering high molecular weight compounds, such as peptides that generally exhibit low buccal absorption rates. These may act by number of mechanisms, such as increasing the fluidity of the cell membrane, extracting inter/intracellular lipids, altering cellular proteins or altering surface mucin. The most common absorption enhancers are azone, fatty acids, bile salts and surfactants such as sodium dodecyl sulfate. Solutions/gels of chitosan were also found to promote the transport of mannitol and fluorescent-labelled dextrans across a tissue culture model of the buccal epithelium while Glycerylmonooleates were reported to enhance peptide absorption by a co-transport mechanism.

MATERIALS AND METHODS
The following chemicals were obtained from different sources and used as received. Pantoprazole was a gift sample from Dr.reddy's labs hydrabad, India; HPMC, PVP, and propylene glycol were obtained from commercial sources. All other chemicals and reagents used were of analytical grade; double-distilled water was used throughout.

Preparation of Pantoprazole-Containing Buccal Patches

The buccal patches composed of different proportions and combinations of HPMC, PVP containing pantoprazole were prepared using a 54-cm2 petridish by solvent casting technique. The polymer solutions were prepared separately and these polymer solutions were poured into drug solution slowly drop by drop and this both solutions were mixed. Permeation enhancers are incorporated in different formulations at different concentration (1%, 3%, 5%). Propylene glycol was incorporated as a plasticizer at concentration of 7% w/w of total formulation and this solution was poured into a Petridish and closed with a funnel in an inverted position and allowed to dry at room temperature at 35°C.

Table 01: Formulation of Pantoprazole Buccal Patches.

COMPOSITION OF FORMULA	PANTOPRAZOLE (Mg)	GELATIN %W/V	HPMC %W/V	PVP %W/V	PG%W/V	SLS %W/V	OLEICACID %W/V	MENTHOL %W/V
F1	40	3	10	30	7	1	-	-
F2	40	-	20	30	7	3	-	1
F3	40	-	30	30	7	5	--	3
F4	40	3	40	30	7	-	1	5
F5	40	3	10	30	7	-	3	-
F6	40	3	20	30	7	-	5	-

Evaluation Of The Pantoprazole Buccal Patch

1. **Measurement of Weight Variation And Thickness**
   The thickness of the patches was assessed at six different points of the patch using thickness gauze (Mitutoyo, Japan). For each formulation, three randomly selected patches ware used. Six films from each batch, as a whole were weighed individually and the average weights are calculated.
2. **Measurement of Folding Endurance**
   The folding endurance was determined manually for the prepared films by repeatedly folding the films at the same place until it broke. The number of times the film could be folded at the same place without breaking or cracking gave the value of folding endurance
3. **Determination of Drug Content**
   The drug contents in the buccal patches were determined by dissolving 1 cm 2 patch in 100ml phosphate buffer saline (pH 7.4) and shaken vigorously for 24 hr at room temperature. These solutions ware filtered through Whatman filter paper (No.42). After proper dilution optical density was measured spectrophotometrically using a UV-VIS spectrophotometer (UV-1700 Double beam spectrophotometer, SHIMADZU Corporation, Japan) at 295 nm against a blank. The drug content was estimated from the calibration curve, which was constructed between 1 and 5 µg/ml concentration ranges. The method was validated for linearity, accuracy and precision.
4. **Determination of Moisture Content**
   The buccal patches were weighed accurately and kept in desiccators containing anhydrous calcium chloride. After 3 days, the patches were taken out was determined by calculating moisture loss (%) using formula 1.
   Moisture content (%) =initial weight- final weight *100/initial weight
5. **Tensile Strength**
   The instrument used to measure the tensile strength designed in our laboratory especially for this project work. The instrument is a modification of the chemical balance used in the normal laboritar. One pan of the balance was replaced with one metallic plate having a hook for attacking the film. The equilibrium of the balance was adjusted by adding weight to the right pan of balance. The instrument was modified in such a way that the patch can be fixed up between two hooks of horizontal beams to hold the test film. A film of 2.5cm length was attached to one side hook of the balance and the other side hook was attached to plate fixed up to the pan as shown in the
   Tensile strength: $T = \frac{M \times g}{B \times t}$ Dynes / Cm^2
   T-force at break / initial cross-sectional area of sample
   Where,
   M- mass in grams
   g- acceleration due to gravity 980 cm/ sec ^{2} 8 breath of the specimen in cm
   t- thickness of the sample in cm
6. **Swelling Index**
   The polymeric films cut in to 1cm * 1 cm were weighed accurately and kept immersed in 50ml of water. The films were taken out carefully at 5, 10, 30, and 60 minutes intervals blotted with filter paper to remove the water present on their surface and weighed accurately the precent swelling calculated using formula.
   Swelling index w2-w1/w1*100
   Where, w1 is the weight of buccal patch before dipping into beaker and w2 is the weight of buccal patch after dipping in beaker and wiped.
7. **Surface pH**
   The surface pH of the patches was determined to investigate possibility of any irritation side in-vivo,

because an acidic or alkaline pH may cause irritation to the buccal mucosa. Therefore the idea the test is to keep the surface pH as close to neutral as possible.

Patches were left to swell for 1 hr on the surface of agar plate, prepared by dissolving 2% agar in warmed phosphate buffer of pH 7.4 under stirring and then set aside till gelling at room temperature. The surface pH paper place on the surface of the swollen patch.

8. Invitro Release Study

The commercially available dialysis membrane (obtained from Sigma Chemicals) was employed for the study, and the in vitro drug release study was carried out using a Franz diffusion cell. The effective diffusion area was 1.8 cm2. The receptor compartment (40 ml) was filled with phosphate buffer saline (PBS), pH 7.4 The patches were applied under occlusion on the dialysis membrane fitted between the donor and receptor compartments of the diffusion cell. The drug release was performed at 37 ± 0.5°C, at a stirring speed of 50 rpm using a magnetic stirrer. Five milliliters of the sample from receptor medium was withdrawn at regular intervals and replaced immediately with an equal volume of phosphate buffer saline, pH 7.4. The amount of pantoprazole released into the receptor medium was quantified by using UV-visible spectrophotometer at 295 nm against a blank.

RESULTS AND DISCUSSION

The main goal of the present investigation efforts was to develop and evaluate new buccal patches comprising a drug containing mucoadhesive polymer layer using polymers like gelatin, pvp and HPMC and study the effects of permeation enhancers. The physicochemical evaluation indicates that all polymer combinations used for fabrication of buccal patches showed good film forming properties and reproducibility. The observation suggest that fabricated films were thin, flexible, elastic, yellow colored smooth and semi translucent the thickness of these formulated buccal patches varied between 0.87± 0.064(F6) and 0.42 ± 0.046(F). The weight variation of these patches varied between 82 ± 0.49 (F2) and 66 ± 0.24(F4) Folding endurance was measured manually. The highest folding endurance was observed in the case of F5 (282) and lowest in the case of F1 (210). The range of folding endurance study ensured flexibility of these formulated buccal patches. The content (%) in all formulations varied between the range 96.29± 0.05 and 91.80±0.12. This indicates that the drug dispersed uniformly throughout the polymeric film. The moisture content (%) study was done for 3 days.

The percentage of moisture content (%) is varied between 7.04(F4) and 3.57(F5). In most cases, the moisture uptake content was found to increase with increasing concentration of polymers that are more hydrophilic in nature. The low moisture content in the formulation is highly appreciable to protect from microbial contamination and bulkiness of the patches. Again, low moisture content in formulation help them to remain stable from being a completely dried and brittle film Tensile strength proves the resistance power of the patch from breaking apart. Tensile strength was measured by using an instrument designed and developed exclusively for the project. It was observed that the tensile strength of various formulations is given in table Swelling behavior of the polymer patches contributes to their ability as prolonged release delivery systems . Good swelling index is also necessary for the effective muco adhesion it was observed that the percentage swelling indices of various formulations or in the range 36-45 Surface pH of all the formulations was determined as described in the methodology chapter. All the formulation were found to have pH7. This reveals that the prepared film would not causes any irritation to buccal mucosa.

Table 02: Physicochemical Evaluation of Pantoprazole Buccal Patches.

S No:	Formulation Code	Weight Variation (gms)	Thickness (mm)	Folding Endurance	Drug Content %	Moisture Content %
1.	F1	68±0.60	0.60±0.098	210	95.98±1.25	5.59
2.	F2	82±0.49	0.7±0.034	225	94.45±1.35	4.28
3.	F3	78±0.78	0.56±0.054	240	96.29±0.05	6.13
4.	F4	66±0.24	0.42±0.046	275	93.14±0.10	7.04
5.	F5	80±0.83	0.65±0.078	282	91.80±0.12	3.57
6.	F6	78±0.78	0.87±0.064	265	93.85±2.01	4.41

Table 3: Tensile Strength,Surface Ph,Swelling Index of *The* Formulations.

PATCH CODE	TENSILE STRENGTH	SURFACE PH	SWELLING INDEX
F1	1800	7	45
F2	1200	7	40
F3	1500	7	36
F4	1600	7	41
F5	1700	7	39
F6	1300	7	43

The invitro drug release pattern of pantoprazole from formulated buccal patches. All of these buccal patches slowely released the drug. The drug released from buccal patches varied from with respect to the polymer composition and concentration of permeation enhancer. An increase in drug release from the buccal patches was found with increasing concentration of permeation enhancers. Among all formulations the maximum in vitro drug release (91.70%). Over a period of 5 hours was and in case of formulations F2, minimum in vitro drug release (83.60 %) was found in the case of formulation F4. The in vitro drug release was more for the pantoprazole buccal patches which were composed with high proportion of HPMC and PVP along with 5% menthol as permeation enhancers.

Table 4; Date Of % Drug Content of The Formulations.

FORMULATION	% DRUG RELEASE
F1	87.47
F2	91.70
F3	86.35
F4	83.60
F5	84.26
F6	88.69

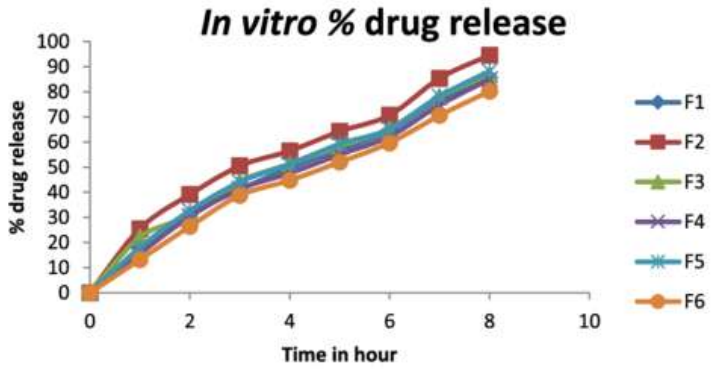

Figure 1: Invitro Release Studies.

CONCLUSION

Buccal patches of pantoprazole using polymers like HPMC and PVP in various proportions and combinations showed satisfactory physiochemical and mucoadhesive characteristics. The proportional amounts of various hydrophilic polymers in various formulations have influence on drug release from these formulated pantoprazole buccal patches. From the present investigation, it can be concluded that such buccal patches 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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