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Design and Evaluation of Buccal Patches of Granisetron Hydrochloride

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ABSTRACT

The goal of the present investigation was to design and evaluate mucoadhesive bilayered buccal devices comprising a drug containing mucoadhesive layer and a drug free backing membrane. Bilaminated films were composed of mixture of drug (granisetron hydrochloride) and chitosan, with hydroxypropyl methylcellulose (15 cps) and backing layer (ethyl cellulose). Films were fabricated by solvent casting technique and were evaluated for thickness, drug content uniformity, in situ bioadhesion strength, tensile strength, percent elongation at break, swelling index, folding endurance and in vitro drug release. Formulation CH_8 containing chitosan and hydroxypropyl methylcellulose (1:1) using propylene glycol (50% by weight of polymer) as plasticizer gave promising results. The optimized film exhibited an in vitro drug release of more than 90% in 5 hours along with satisfactory bioadhesive strength and tensile strength. This promising film was tested for short-term stability for three months at 30±2^{0}C and 40±2ºC/75±5% relative humidity and drug-excipient interaction (FTIR). Stability study of the above formulation indicated that there is no significance change in drug content ($p<0.05$). FTIR spectra indicated that there are no drug-excipient interactions.

Keywords*: Granisetron hydrochloride; hydroxypropyl methylcellulose; chitosan; polyvinyl pyrrolidone; mucoadhesive buccal films.*

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to promptly achieve and then maintain the desired concentration[1]. Controlled release drug administration means not only prolonged duration of drug delivery, as in sustained release / prolonged release, but also implies predictability and reproducibility of drug release kinetics[2]. The need is not only of reproducibility and predictability of drug release kinetics but also patient compliance.

Granisetron hydrochloride (5 HT_3 receptor antagonist) is a drug used in the management of nausea and vomiting induced by cytotoxic chemotherapy and for prevention and treatment of post-operative nausea and vomiting[3,4]. The drug is well absorbed from the gastrointestinal tract, but its oral bioavailability is low (60%) due to extensive first-pass metabolism. Since buccal route bypasses first-pass effect, the dose of granisetron hydrochloride (GRN) could be reduced by 50%. The physico-chemical properties of GRN, its suitable biological half-life (3-4 h) and low molecular weight (348.9) make it suitable candidate for administration by buccal route. There are several reported studies on administration of drugs via buccal route, as patches or discs[5-9]. Buccal films of GRN were fabricated by solvent casting technique and were evaluated for thickness, drug content uniformity, *in situ* bioadhesion strength, tensile strength, percent elongation at break, swelling index, folding endurance and *in vitro* drug release

MATERIALS AND METHODS

Materials:

Granisetron hydrochloride (GRN) and chitosan (65 cps) were generous gifts from Cipla, Vikhroli and Central Institute of Fisheries Technology, Cochin, respectively. The polymers hydroxypropyl methylcellulose (HPMC 15 cps), ethylcellulose (EC), polyvinyl pyrrolidone (PVP K-30) and propylene glycol were procured from SD Fine

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Chemicals, Boisar, Maharashtra (India).

Method of preparation of buccal patches:

Buccal patches containing drug reservoir were prepared by solvent casting technique[10]. PVP (16.7% by weight of polymers) was used as mucoadhesive polymer and propylene glycol (30-50% of the polymer weight) as plasticizer.

The weighed quantity of HPMC was properly dispersed in aqueous acetic acid solution (1% v/v, 25 ml). Then weighed quantity of chitosan was taken and mixed with the above solution. It was kept aside for 24 h and then the solution was filtered through fine muslin cloth (#80 mesh) to remove undissolved portion of chitin. PVP was accurately weighed and dissolved in the filtered solution. The required quantity of plasticizer propylene glycol and aspartame (2% by weight of polymers) were added. Then the drug was dispersed uniformly in the viscous solution with continuous stirring. The resultant mixture was poured into specially fabricated glass moulds (5x5 cm) lined with aluminum foil. Drying was carried out at room temperature for 24 h. The drying rate was controlled by placing an inverted glass funnel. This arrangement also controlled the effect of air-current on the films. For complete drying, the moulds were kept in a hot-air oven maintained at 45±1º for another 12 h. After complete drying, the films were removed from the glass moulds. The films were smooth, flexible and could be cut to any desired size and shape. Small patches of (1 x 1 cm in size) containing 1.12 mg of granisetron hydrochloride (equivalent to I mg granisetron) were cut with the help of sharp pen knife. The compositions of various patches prepared are shown in Table 1. A rate controlling membrane was also casted on glass mould using the polymer EC (4% w/v) using alcohol:toluene in 1:4 ratio as a solvent, containing glycerol 10% by weight of polymer as plasticizer. A membrane of 1 x 1 cm was cut and one side of drug reservoir was sealed using this membrane for unidirectional release of drug.

Evaluation of buccal patches:

Thickness of the films was determined using a micrometer screw gauge. Bioadhesive strength of all the formulations was tested; i.e., weight required to pull off the formulation from mucus tissue is recorded as mucoadhesion/bioadhesion strength in g (Table 2). This parameter for the film was measured on a modified physical balance[11,12] using bovine cheek pouch as model mucosal membrane (Fig. 1). A self designed and locally fabricated apparatus (Fig. 2) was used for determination of tensile strength and percent elongation at break, which measure the mechanical strength of the film. A small film strip (5 cm x 1 cm) was pulled by using weight at a rate of 10 g/min, till patch breaks apart into two pieces. The initial and final length of the strip was noted and tensile strength and percent elongation at break was calculated using the formula as suggested by Khanna R et al[13].

$$\text{Tensile strength} = \frac{\text{Force at break}}{\text{Initial cross sectional area}} \text{ dynes/cm}^2$$

$$\text{Percent elongation at break} = \frac{\text{Increase in length}}{\text{Initial Length}} \times 100$$

Folding endurance of the film was determined by repeatedly folding a small strip of film (2 cm x 2 cm) at same place till it broke. The number of times the film could be folded at the same place, without breaking, gave the value of folding endurance. For swelling index, buccal strips of equal size (1x1 cm) were weighed accurately and kept immersed in 50 ml of water. Strips were taken out carefully at 5, 10, 30 and 60 minute intervals, blotted with filter paper to remove water present on their surface and weighed accurately. The percent swelling was calculated using the formula as suggested by Ilango R et al[14].

$$\text{Swelling Index} = \frac{\text{Wet Weight - Dry Weight}}{\text{Wet Weight}} \times 100$$

Drug content uniformity:

The content uniformity and drug content of the buccal patches were determined as described by Satishbabu BK et al[8] and Patel VM et al[16]. The film of known weight (0.5 x 0.5 cm) was extracted with 25 ml of distilled water by shaking for 1 h on a rotary flask shaker (KEMI, Ernakulam, Kerala) at 100 rpm. The solution is suitably diluted with distilled water and absorbance was measured in UV spectrophotometer at 302 nm against solvent blank (distilled water). The mean drug content and standard deviations (n = 3) for all the designed films were calculated.

***In vitro* drug release studies:**

In vitro drug release study was carried out using the beaker method as described by Ilango R et al[14]. The buccal film affixed with the backing membrane was held at the centre of a microscopic slide by means of rubber band. The slide was placed at an angle of 45º in 250 ml beaker containing 200 ml of pH 6.8 phosphate buffer preheated at 37º and the beaker was kept in water bath maintained at 37±2º. A non-agitated system was selected to eliminate any effect of turbulence on the release rate to assure that no disruption of strip occurred. Periodic assay samples were obtained by removing the slide, stirring the sample, pipetting a 5 ml sample with pipette whose tip was covered with a piece of muslin cloth. The slide was quickly reinserted making sure that the strip remained completely immersed throughout release rate studies. The beaker was kept covered throughout the run to prevent evaporation of dissolution medium. All samples were analyzed spectrophotometrically at 302 nm for GRN.

RESULTS AND DISCUSSION

In the present work attempt has been made to prepare buccal films of granisetron hydrochloride, an anti-emetic drug (5-HT_3 antagonist). A total of nine mucoadhesive patches of GRN were prepared and evaluated for biological, physical and mechanical parameters. According to work plan, the films were evaluated for their appearance, surface texture, thickness, weight variation, folding endurance, swelling index, tensile strength, elongation at break, *in situ* bioadhesion strength, drug content uniformity, *in vitro* drug release, short-term stability and drug-excipient interaction.

The surface texture of buccal patches was smooth and uniform. Colour of the patches changes from white to yellowish white as we go on increasing the concentration of chitosan from 33.3 to 66.7% w/w of total polymer concentration. The thickness and weight of the films were found to be uniform as indicated by the low values of standard deviation.

Initially blank films were prepared in order to determine the best possible combination of polymers, plasticizers and solvents required to obtain satisfactory formulations. Then the formulations, which showed completely homogenous, smooth, flexible and non-sticky surface were selected for further studies and evaluated for various parameters as mentioned earlier. The results revealed that the release of drug is dependent on polymer ratio as well as on plasticizer (PG) concentration.

The films were quite flexible as shown by measurement of folding endurance (Table 2). The folding endurance of films goes on increasing as we increase the concentration of HPMC or propylene glycol. The maximum folding endurance as shown by formulation CH_7 is approximately 135. There was significant correlation between tensile strength and polymer composition. The tensile strength of film increases as we increase the concentration of chitosan and plasticizer concentration does not have much effect (Fig. 3). The mucoadhesivity (*in vitro* bioadhesion strength) of all the films of varying ratios of polymers was tested and was found to increase as the proportion of chitosan in the film increases (Fig. 4). This may be due to the fact that positive charges on the surface of chitosan could give rise to strong electrostatic interaction with mucus or negatively charged mucous membrane[15]. The mean drug content of the films (Table 2) was found to be within the range of 96.24 – 99.21 percent and the low values of standard deviation indicate uniform distribution of the drug within the prepared films.

Drug release from the films was found to be largely dependent on polymer ratio and plasticizer concentration and increases with an increase in the concentration of HPMC and plasticizer (Fig. 5). The *in vitro* release paramater values, $t_{50\%}$ and $t_{70\%}$ (Table 3) displayed by the various formulations range from 1.52 to 2.26 h and 2.75 to 4.50 h respectively. When the data was plotted as log cumulative percent of drug remained versus time, the plots obtained were linear, with 'r' values ranging from 0.980 to 0.997 indicating that the release followed first order kinetics. The *in vitro* drug release data were fitted into Higuchi's and Peppa's models to determine the mechanism of drug release and swellability of polymer matrix. When the data was plotted according to Higuchi's equation, i.e. cumulative percent of drug released versus square root of time, the plots were linear, with 'r' values ranging from 0.988 to 0.997 indicating that the release of drug from films occurs by diffusion mechanism. When the data was treated according to Peppa's equation, the 'n' values of all formulations were found to be $0.5<n<1$ which indicates non-Fickian release mechanism.

Formulation CH_8 containing chitosan and HPMC in 1:1

ratio with a plasticizer concentration of 50% by weight of polymer has shown promising results and displayed $t_{50\%}$ and $t_{70\%}$ values of 1.75 and 2.75 h respectively and released more than 90% of drug in 5 h and it has got reasonably good tensile strength and mucoadhesive properties

Drug-excipient interactions were ruled out by IR spectroscopic studies (Fig. 6) using Perkin-Elmer IR spectrophotometer by potassium bromide pellet method. Short-term stability studies on the promising formulation CH_8revealed no appreciable changes in drug content at room temperature (30±2º) and at 40±2º/75% RH when stored over a period of 90 days.

CONCLUSION

The results of the present study indicated that buccal patches of the drug GRN can be successfully prepared using a combination of chitosan and HPMC (15cps). The formulation CH_8 (containing the above polymers in a ratio of 1:1 and plasticizer concentration of 50% by weight of polymer) has emerged as the promising buccal drug delivery system of GRN and displayed $t_{50\%}$ and $t_{70\%}$ values of 1.75 and 2.75 h respectively and released more than 90% of the drug in 5 h, with reasonably good tensile strength and mucoadhesive properties.

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Figure 1: Bioadhesion testing apparatus

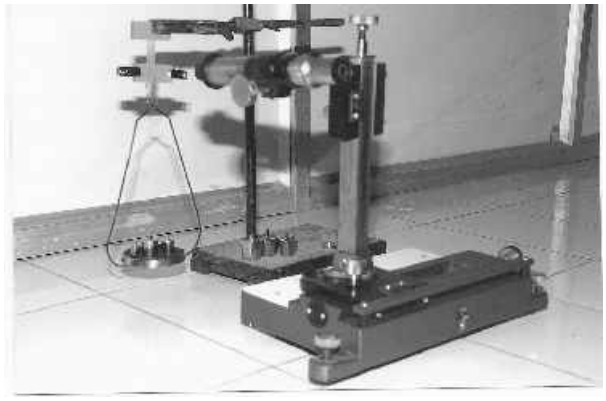

Figure 2: Tensile strength testing apparatus

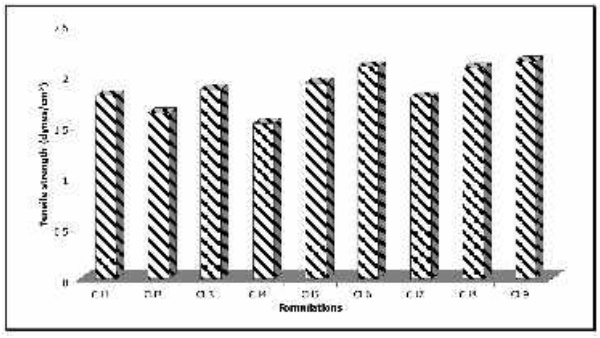

Figure 3: Tensile strength studies

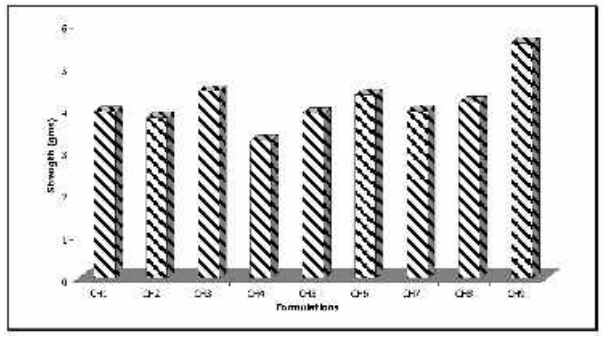

Figure 4: In situ studies on mucoadhesion strength

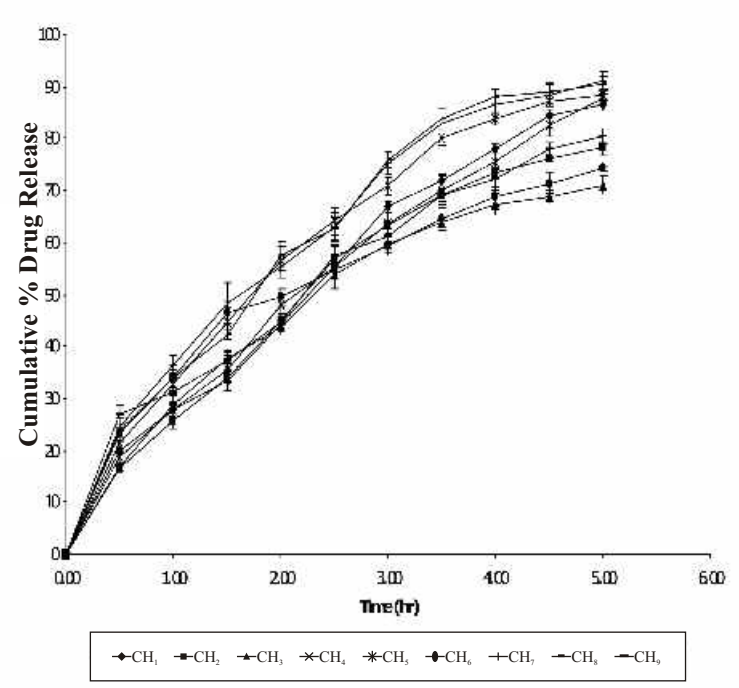

Figure 5: In vitro drug release profiles of formulations CH_1 to CH_9

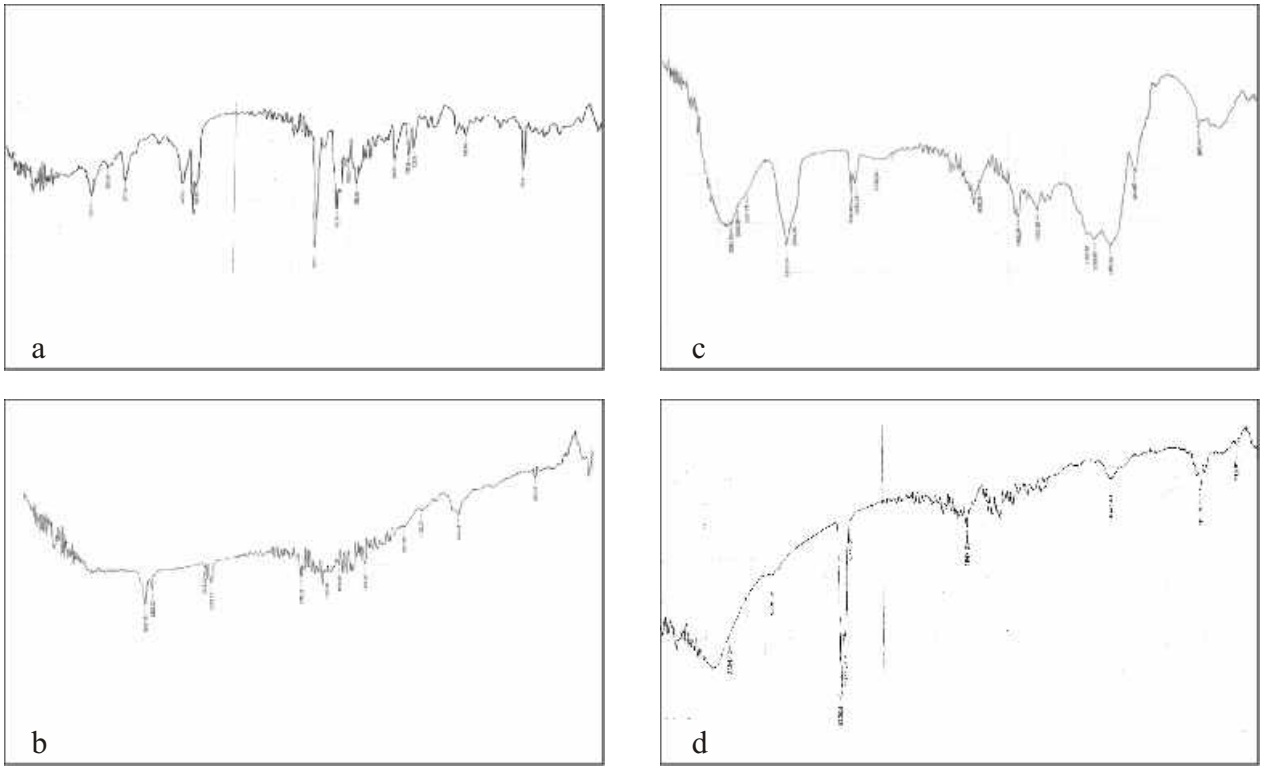

Figure 6: FTIR spectra of (a) granisetron hydrochloride, (b) chitosan, (c) HPMC 15cps and (d) promising formulation CH_8

Table 1: Composition of buccal patches *

Formulation Code	Chitosan-HPMC Ratio	Chitosan-(mg)	HPMC (mg)	Propylene glycol *(mg)*
CH_1	1:2	250	500	225
CH_2	1:1	375	375	225
CH_3	2:1	500	250	225
CH_4	1:2	250	500	300
CH_5	1:1	375	375	300
CH_6	2:1	500	250	300
CH_7	1:2	250	500	375
CH_8	1:1	375	375	375
CH_9	2:1	500	250	375

HPMC- Hydroxy Propyl Methyl Cellulose (15 cps), PVP - Polyvinyl Pyrrolidone
**** The Quantities of drug (Granisetron hydrochloride), PVP, aspartame and acetic acid solution (1% v/v) are 28mg, 125mg, 15mg and 25ml re***

Table 2: Evaluation of buccal patches

Film Code	Mean Thickness* (mm)	Mean Weight* (mg)	Folding endurance*	Swelling Index*	Tensile Strength* (dynes/ cm^2x10^7)	Elongation At break* (%)	In vitro Biadhesion Strength* (gm)	Mean Drug Content %
CH_1	0.20 (0.01)	9.77 (0.36)	92.66 (4.50)	45.60 (0.36)	1.79 (0.03)	5.01 (0.078)	3.93 (0.15)	97.96 (2.28)
CH_2	0.30 (0.02)	10.29 (0.36)	74.00 (4.72)	38.10 (0.36)	1.62 (0.08)	4.30 (0.051)	3.80 (0.20)	96.36 (1.64)
CH_3	0.22 (0.01)	10.26 (0.35)	52.66 (4.72)	36.90 (0.35)	1.86 (0.09)	5.75 (0.070)	4.43 (0.21)	96.40 (0.76)
CH_4	0.23 (0.01)	9.81 (0.28)	117.66 (2.51)	49.40 (0.28)	1.52 (0.06)	3.17 (0.075)	3.25 (0.13)	98.16 (1.42)
CH_5	0.29 (0.03)	11.70 (0.38)	83.33 (3.51)	40.60 (0.38)	1.92 (0.03)	5.04 (0.41)	3.90 (0.23)	96.24 (0.52)
CH_6	0.23 (0.02)	10.68 (0.40)	60.00 (4.58)	38.25 (0.40)	2.08 (0.10)	6.57 (0.231)	4.33 (0.15)	96.33 (0.72)
CH_7	0.22 (0.02)	9.91 (0.33)	135.66 (4.50)	47.15 (0.40)	1.78 (0.02)	6.09 (0.133)	3.96 (0.16)	96.90 (1.89)
CH_8	0.34 (0.03)	11.75 (0.40)	99.38 (5.13)	43.60 (0.33)	2.06 (0.04)	7.18 (0.032)	4.16 (0.09)	99.21 (0.55)
$CH9_2$	0.20 (0.02)	9.86 (0.22)	79.33 (6.50)	33.80 (0.22)	2.13 (0.07)	7.31 (0.096)	5.56 (0.16)	96.78 (0.51)

** Average of three determinations, values shown in parenthesis are standard deviations.*
Formulation CH_8 was selected as the best and used for further studies.

Table 3: In vitro drug release parameters

Sl. No.	Formulation code	$t_{50\%}$ (h)	$t_{70\%}$ (h)	Cumulative % Drug release in 5h* ±SD
1	CH_1	2.25	3.30	86.50±1.28 2
2	CH_2	2.25	3.60	78.18±1,28 3
3	CH_3	2.26	4.50	71.07±1.76 4
4	CH_4	1.75	3.00	88.46±1.00 5
5	CH_5	2.24	3.50	87.85±1.32 6
6	CH_6	2.21	4.25	79.27±0.50 7
7	CH_7	1.52	2.80	91.25±1.73 8
8	CH_8	1.75	2.75	90.37±1.73 9
9	CH_9	2.15	3.75	80.49±1.62

$t_{50\%}$ and $t_{70\%}$ are time for 50% and 70% drug release respectively. ****Average of three determinations***
SD - standard deviation

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