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Formulation Design and Evaluation of Bilayer Buccal Tablets of Granisetron Hydrochloride

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ABSTRACT

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In the present study, an attempt was made to design and evaluate bilayer buccal tablets of granisetron hydrochloride (an anti-emetic drug), in order to overcome bioavailability problems, to reduce dose dependent side effects and frequency of administration. Bilayer buccal tablets containing the drug were prepared by direct compression method using combination of polymers (such as sodium alginate, HPMC 50 cps and Carbopol 934p) and ethyl cellulose as an impermeable backing layer to release the drug in a unidirectional way toward the mucosa, thus avoiding loss of drug due to wash out by saliva. The designed tablets were evaluated for various physical and biological parameters, drug content uniformity, *in-vitro* drug release, short-term stability, drug- excipient interactions (FTIR). The formulation SAF_1 with the drug matrix layer composition- sodium alginate (47% w/w), Carbopol 934p (3% w/w), PVP K-30 (binder, 30% w/w) and mannitol (channeling agent, 15% w/w) was found to be promising. This optimized formulation exhibited an *in vitro* drug release of 94% in 8 h along with satisfactory bioadhesion strength (4.6 gm). Short-term stability studies (40±2° C/75±5% RH for 3 months) on the promising formulation indicated that there are no significant changes in drug content and *in vitro* dissolution characteristics ($p<0.05$). IR spectroscopic studies indicated that there are no drug-excipient interactions.

Keywords: Granisetron hydrochloride, buccal tablets, sodium alginate, HMPC 50 cps and Carbopol 934p.

INTRODUCTION

In recent years, there has been a growing interest in the use of delivery of therapeutic agent through various transmucosal routes to provide a therapeutic amount of drug to the proper site in body to promptly achieve and then maintain the desired concentration[1].

The unique environment of the oral cavity offers its potential as a site for drug delivery. Because of the rich blood supply, higher bioavailability, lymphatic drainage and direct access to systemic circulation, the oral mucosal route is suitable for drugs which are susceptible to acid hydrolysis in the stomach or which are extensively metabolized in the liver. The thin mucin film, which exists on the surface of the oral mucosa, may provide an opportunity to retain a drug delivery system in contact with the mucosa for prolonged period, if it is designed to be mucoadhesive. Such system ensures close contact with absorbing membrane, thus optimizing the drug concentration gradient across the biological membrane and reducing the differential pathway. Therefore, the oral mucosa may be potential site for controlled or sustained drug delivery. The permeability of the oral mucosa is low; hence, the oral mucosa could be utilized to potent drugs which are required in small doses[2].

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Nausea and vomiting are common complications of multiple conditions, and adversely affect quality of life. Various mechanisms, both peripheral and central are known to play a role in the emergence of nausea and vomiting[3]. There are a number of commonly used agents in the clinical practice for the treatment of emesis (e.g., anticholinergics, antihistamines, phenothiazines, butyrophenones, benzamides and $5\text{-}HT_3$ receptor antagonists), which differ in their efficacy and safety profiles in various emetogenic conditions ranging from gastroenteritis to chemotherapy-induced nausea and vomiting.

With the advances in pathophysiology of nausea/vomiting, the older antiemetics like dopamine receptor antagonists, e.g., metoclopramide or domperidone are now being largely replaced by serotonin receptor antagonists, because of their comparatively limited efficacy and risk of adverse effects.

Granisetron hydrochloride (GRN) is a novel anti-emetic and anti-nauseant drug. It is a selective serotonin ($5\text{-}HT_3$) receptor antagonist with little or no affinity for other serotonin, beta-adrenergic, dopamine or histamine receptors. During chemotherapy-induced vomiting, mucosal

enterochromaffin cells release serotonin, which stimulates 5-HT_3 receptors. The stimulation of 5-HT_3 receptors by serotonin causes vagal discharge resulting in vomiting. Granisetron blocks serotonin stimulation and subsequent vomiting[4]. Granisetron is more effective than ondansetron when used in combination with dexamethasone in the prevention of acute and delayed vomiting caused by high emetogenic chemotherapy[5].

GRN is well absorbed from the gastrointestinal tract, but its oral bioavailability is low (60%) due to extensive first-pass metabolism[6,7]. Since buccal route bypasses first-pass effect, the dose of granisetron hydrochloride could be reduced by 50%. The physico-chemical properties of granisetron, such as high aqueous solubility, its long duration[8] of action (24 h) and low molecular weight (348.9) make it suitable candidate for once a day administration by buccal route. Granisetron noncompetitively binds to the 5-HT_3 receptor and is associated with a long duration of action as shown by the inhibition of a 5-HT axonal response flare for up to 24 h. Buccal delivery offers a safer mode of drug utilization, since drug absorption can be promptly terminated in cases of toxicity by removing the dosage form from the buccal cavity[9]. A suitable buccal drug delivery system should possess good bioadhesive properties, so that it can be retained in the oral cavity for the desired duration. In addition, it should release the drug in a unidirectional way toward the mucosa (to avoid loss of drug due to wash out by saliva), in a controlled and predictable manner, to elicit the required therapeutic response. This unidirectional drug release can be achieved using bilayer devices[10].

Hence, the aim of the present study was to design and evaluate bilayer buccoadhesive tablets of GRN that could be applied to the buccal mucosa to release the drug unidirectionally in order to avoid first pass effect for improvement in bioavailability and to enhance patient compliance.

MATERIALS AND METHODS

The drug GRN was received as a gift sample from Cipla Pharma Ltd, Vikhroli, Mumbai. Sodium alginate (SA), HMPC 50 cps (HPMC), Carbopol 934p (CP), polyvinyl pyrrolidone K-30 (PVP), polyethylene glycol 4000 (PEG), ethylcellulose (EC) and D-mannitol (DM) were procured from SD Fine Chem., Mumbai.

Preparation of buccal tablets[11]:

Direct compression method has been employed to prepare buccal tablets of GRN using sodium alginate (SA), HMPC 50 cps (HPMC) and Carbopol 934p (CP) as polymers.

Method: All the ingredients including drug, polymers and excipients were weighed accurately according to the batch formula (Table 1). The drug is thoroughly mixed with mannitol on a butter paper with the help of a stainless steel spatula. Then all the ingredients except lubricants were mixed in the order of ascending weights and blended for 10 min in an inflated polyethylene pouch. After uniform mixing of ingredients, lubricant was added and again mixed for 2 min. The prepared blend (100 mg) of each formulation was pre-compressed, on 10-station rotary tablet punching machine (Clit, Ahmedabad) at a pressure of 0.5 ton for 30 s to form single layered flat-faced tablet of 9 mm diameter. Then, 50 mg of ethyl cellulose powder was added and final compression was done at a pressure of 3.5 tons for 30 s to get bilayer tablet. Compositions of the designed bilayer tablets are given in Table 1.

Evaluation of buccal tablets:

Twenty tablets were selected at random and weighed individually. The individual weights were compared with the

Table 1: Composition of buccal tablets

Ingredients* (mg/tablet)	Formulation Code					
	SAF_0	SAF_1	SAF_2	HPF_0	HPF_1	HPF_2
Granisetron hydrochloride	1	1	1	1	1	1
Sodium alginate	50	47	44	-	-	---
HPMC 50 cps	-	-	-	50	47	44
Carbopol 934 p	-	3	6	-	3	6
PVP K-30	30	30	30	-	-	-
D-mannitol	15	15	15	45	45	45
Aspartame	2	2	2	2	2	2
PEG-4000	2	2	2	-	-	-
Magnesium stearate	-	-	-	2	2	2
Ethyl cellulose	50	50	50	50	50	50
Total	150	150	150	150	150	150

*HPMC-Hydroxypropyl methylcellulose, PVP-Polyvinyl pyrrolidone, PEG-Polyethylene glycol

average weight for determination of weight variation. Hardness and friability of the tablets were determined by using Monsanto hardness tester and Roche friabilator respectively. For content uniformity test, 10 tablets were weighed and powdered. The powder equivalent to 1 mg of drug was extracted in to distilled water, filtered through 0.45µm membrane filter disc (Millipore Corporation) and analyzed for GRN after appropriate dilution by measuring the absorbance at 302 nm, against solvent blank. The drug content was calculated using the standard calibration curve. The mean percent drug content was determined as an average of three determinations. The surface pH of the buccal tablets is determined in order to investigate the possibility of any side effects *in vivo*. A combined glass electrode is used for this purpose. The tablet is allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.8 0.05) for 2 h at room temperature. The pH is identified by bringing the electrode into contact with the tablet surface and allowing to equilibrate for 1 min[8]. The swelling index of the buccal tablet is evaluated by using pH 6.8 phosphate buffer. The initial weight of the tablet is determined (w_1). The tablets is placed in pH 6.8 phosphate buffer (6 ml) in a Petri-dish placed in an incubator at 37±1° C and tablet is removed at different time intervals (0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0 and 8.0 h), blotted with filter paper and reweighed (w_2)[12]. The swelling index is calculated using the formula: Swelling index = 100 (w_2-w_1) / w_1. 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 tablets was measured on a modified physical balance[13-16] using bovine cheek pouch as model mucosal membrane (Fig. 1).

***In vitro* drug release study[11]:**

This is carried out in USP XXIII tablet dissolution test apparatus-II (Electrolab TDT-06N), employing paddle stirrer at 50 rpm and 200 ml of pH 6.8 phosphate buffer as dissolution medium. The release study is performed at 37±0.5° C. The backing layer of the buccal tablet is attached to glass disk with cyanoacrylate adhesive. The disk is placed at the bottom of the dissolution vessel. Samples of 5 ml were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through 0.45µm membrane filter disc (Millipore Corporation) and analyzed for GRN after appropriate dilution by measuring the absorbance at 302 nm. The experiment was run in triplicate.

Fig.1: Bioadhesion testing apparatus

Stability studies:

Short- term stability studies were performed at a temperature of 40 ± 2° C / 75±5% RH over a period of 3 mo (90 d) on the promising buccal tablet of granisteron hydrochloride (formulation SAF_1). Sufficient number of tablets (15) were packed in amber colored rubber stoppered vials and kept in stability chamber maintained at 40± 2° C / 75±5% RH. At intervals of 1 mo, the tablets were visually examined for any physical changes, changes in drug content and at the end of 3 mo period, they were also tested for *in vitro* drug release pattern and the results were subjected to statistical analysis using student't' test.

Drug-excipient interaction study:

FTIR spectra of the drug, promising formulations and polymers were obtained by potassium bromide pellet method using Perkin-Elmer FTIR series (model-1615) spectrophotometer in order to rule out drug-excipient interactions.

RESULTS AND DISCUSSION

The main goal of this work was to develop new mucoadhesive bilayer buccal tablets of GRN, an anti-emetic drug (5-HT_3 antagonist), consisting of drug free non- adhesive protective layer. The double layered structure design was expected to provide drug delivery in an unidirectional fashion to the mucosa and to avoid loss of drug due to wash out by saliva, release drug immediately to produce a prompt pharmacological action and remain in oral cavity and provide a sustained release of enough drug over an extended period of time. A total of six formulations of mucoadhesive buccal tablets of GRN were prepared and evaluated for biological, physical and mechanical parameters. According to work plan, the tablets were evaluated for their thickness, hardness, friability, weight variation, swelling index, surface pH, drug content and mucoadhesive strength (Table 2).

The appearance of buccal tablets was smooth and uniform on physical examination. The hardness of prepared buccal tablets of GRN was found 3.2 to 4.8 kg/cm^2; hardness increases with increasing CP proportion in the formulation. Mean thickness and weights were found to be uniform as

Table 2: Evaluation of buccal tablets

Formulation code	Mean hardness*	Mean thickness* (kg/cm^2)	Weight variation* (mm)	Friability (%) (mg)	Mean % drug content	Surface pH*	Swelling Index* (after 8 h)	Mucoadesive sterngth (gm)
SAF_0	3.6 (0.58)	2.00 (0.06)	148 (0.30)	0.62 (0.16)	94.65 (0.76)	6.53 (0.11)	19.57 (1.76)	4.33 (0.05)
SAF_1	4.7 (0.95)	2.10 (0.08)	150 (0.50)	0.71 (0.05)	96.98 (0.86)	6.06 (0.05)	34.03 (2.67)	4.62 (0.06)
SAF_2	4.8 (0.87)	2.05 (0.10)	152 (0.63)	0.82 (0.06)	95.49 (1.02)	5.97 (0.07)	42.53 (2.10)	4.90 (0.10)
HPF_0	3.2 (0.65)	2.00 (0.05)	149 (0.35)	0.82 (0.03)	94.47 (0.84)	6.30 (0.08)	24.20 (2.28)	3.83 (0.06)
HPF_1	3.6 (0.55)	2.00 (0.08)	150 (0.20)	0.77 (0.06)	93.87 (0.76)	5.65 (0.13)	45.36 (2.37)	4.20 (0.12)
HPF_2	3.8 (0.60)	2.10 (0.06)	151 (0.30)	0.81 (0.08)	95.67 (1.34)	5.83 (0.16)	56.43 (1.40)	4.60 (0.12)

*Average of three determinations, values shown in parenthesis are standard deviations. SAF and HPF indicate buccal tablets using sodium alginate or HPMC 50cps as mucoadhesive polymers respectively. SAF_0 and HPF_0 are control formulations without Carbopol 934p. Formulation SAF_1 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)	$t_{90\%}$ (h)	Cumulative % drug release in 8 h*±SD
1.	SAF_0	1.95	4.05	6.85	97.24±1.16
2.	SAF_1	2.50	4.50	7.40	94.18±1.16
3.	SAF_2	2.80	5.18	>8.00	89.39±1.56
4.	HPF_0	2.55	3.83	6.65	96.21±0.76
5.	HPF_1	3.55	5.35	7.90	90.91±1.07
6.	HPF_3	4.00	6.00	>8.0	87.62±1.58

$t_{50\%}$, $t_{70\%}$ and $t_{90\%}$ are time for 50%, 70% and 90% drug release respectively.
*Average of three determinations

indicated by the low values of standard deviation. The thickness and weight of the prepared buccal tablets were found to be in the range of 2.00 to 2.10 mm and 148 to 152 mg respectively. Friability values less than 1% indicate good mechanical strength to withstand the rigors of handling and transportations. Results are given in Table 2. The drug content of buccal tablets was quite uniform as seen in the above mentioned table. The average drug content of the buccal tablets was found to be within the range of 93.87 to 96.98 % and the low values of standard deviation and coefficient of variation (<2) indicate uniform distribution of the drug within the prepared buccal tablets. The surface pH was determined in order to investigate the possibility of any side effects, in the oral cavity as acidic or alkaline pH is bound to cause irritation to the buccal mucosa. Surface pH of all formulations was found to be in the range of 5.65 to 6.53. Hence it is assumed that these formulations cause no irritation in the oral cavity.

The swelling profile of different batches of the tablets is shown in Table 2. These profiles indicate the uptake of water into the tablet matrix, producing an increase in weight. The swelling state of the polymer (in the formulation) was reported to be crucial for its bioadhesive behavior. Adhesion occurs shortly after the beginning of swelling but the bond formed between mucosal layer and polymer is not very strong. The adhesion will increase with the degree of hydration until a point where over-hydration leads to an abrupt drop in adhesive strength due to disentanglement at the polymer/tissue interface. Results indicate that as the concentration of CP increases the swelling index increases.

The mucoadhesive strength of buccal tablets was found to be maximum in case of formulation SAF_2 i.e. 4.90 gm. This may be due to fact that positive charges on surface of CP could give rise to strong electrostatic interaction with mucous or negatively charged mucus membrane.

Comparatively, the buccal tablets containing SA as the matrix

polymer have displayed greater hardness (3.6 to 4.8 kg/cm^2), mucoadhesive strength (4.33 to 4.90 g) surface pH (5.97 to 6.53); less friability (0.62 to 0.82%) and swelling indices (19.57 to 42.53) than those of HPMC, which showed 3.2 to 3.8 kg/cm^2, 3.83 to 4.60 g and 5.65 to 6.30; 0.77 to 0.82% and 24.20 to 56.43 values for the above parameters respectively.

***In vitro* drug release:**

In vitro drug release studies were carried out in USP XXIII tablet dissolution test apparatus-II employing paddle stirrer at 50 rpm and 200 ml of pH 6.8 phosphate buffer as dissolution medium. From dissolution data it is evident that the designed formulations have displayed more than 87% drug release in 8 h. Comparatively the buccal tablets containing SA as the matrix polymer have displayed greater drug release in 8 h (89.39 to 97.24%) than those of HPMC (87.62 to 96.21%). Similarly, the former have shown faster drug release rates ($t_{50\%}$ values ranging from 1.95 to 2.80 h) than the latter ($t_{50\%}$ values ranging from 2.55 to 4.0 h). The formulation SAF_1 with the drug matrix layer composition- SA (47% w/w), CP (3%w/w), PVP (30% w/w) and DM (channeling agent, 15% w/w) was found to be promising, which showed $t_{50\%}$, $t_{70\%}$ and $t_{90\%}$ values of 2.5 h, 4.5 h and 7.4 h respectively and released 94% drug within 8 h (Table 3). This formulation showed satisfactory mucoadhesion (4.6 g). The designed bilayer buccal tablets have a novel approach, which could be considered as superior dosage form than the conventional marketed tablet formulations.

In vitro drug release profiles of the designed formulations are depicted in Figs. 2 and 3. Comparison of dissolution parameters ($t_{50\%}$, $t_{70\%}$ and $t_{90\%}$) of the buccal tablets of GRN displayed in Fig. 4.

Drug release kinetics:

In vitro drug release data of all the buccal tablet formulations of GRN was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetics and according to Higuchi's and Peppas models to ascertain mechanism of drug release. It was evident that all the formulations displayed zero-order release kinetics ('r' values from 0.9608 to 0.9951). Higuchi and Peppas data reveals that the drug is released by non-Fickian diffusion mechanism ('r' values from 0.9821 to 0.9996 and 'n' values from 0.682 to 0.821).

Fig.2: *In vitro* drug release profiles of formulations using sodium alginate as mucoadhesive polymer

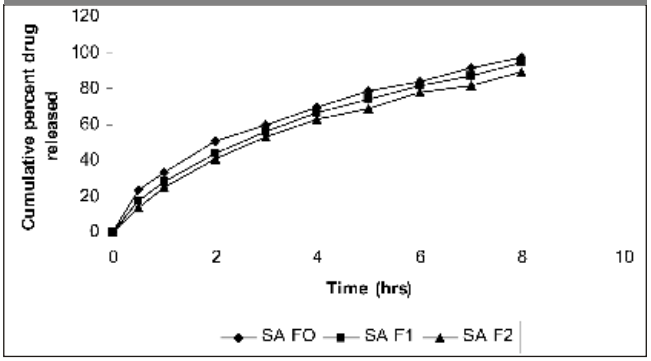


Fig.3 : *In vitro* drug release profiles of formulations using HPMC as mucoadhesive polymer

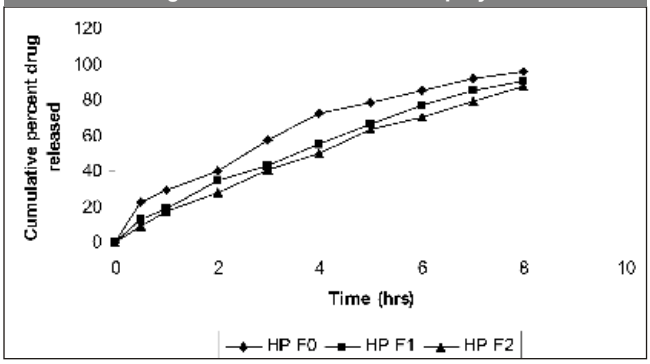
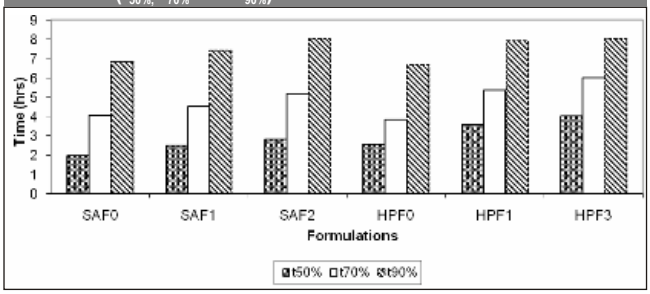


Fig. 4: Comparison of dissolution parameters ($t_{50\%}$, $t_{70\%}$ and $t_{90\%}$) of buccal tablets of GRN.



The IR spectrum of the pure drug GRN displayed characteristic peaks at 3230, 1645 and 1551 cm^{-1} due to -NH, C=O and -CN stretchings respectively. All the above characteristic peaks were also found in the IR spectrum of the formulation SAF_1. The presence of above peaks confirms undisturbed structure of drug in the above formulation. Hence, there are no drug-excipient interactions.

From the stability studies data it can be seen that the drug content of the formulation SAF_1 was not significantly effected at 40 ± 2° C / 75 ± 5% RH after storage for 3 mo. Statistical analysis of the drug content data (by student 't' test) gives 't' value of 1.31 which is much less compared to the table value of 4.3 ($p<0.05$).

CONCLUSION

The results of the present study indicate that bilayer buccal tablets of GRN with controlled drug release can be successfully prepared by direct compression method using SA and CP as mucoadhesive polymers and EC as backing layer to provide unidirectional release of the drug. The

formulation SAF_1 with the drug matrix layer composition- SA (47% w/w), CP (3%w/w), PVP (30% w/w) and DM (channeling agent, 15% w/w) was found to be promising, which shows an *in vitro* drug release of 94% in 8 h along with satisfactory bioadhesion strength (4.6 g).

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