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DESIGN AND EVALUATION OF BUCCOADHESIVE BILAYER TABLETS OF GRANISETRON HYDROCHLORIDE

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ABSTRACT

Purpose of Study: In the present study, an attempt was made to design and evaluate buccoadhesive bilayer tablets of granisetron hydrochloride (an anti-emetic drug), in order to overcome bioavailability problems, to reduce dose dependent side effects and frequency of administration.

Method: Bilayer buccal tablets containing the drug were prepared by direct compression method using combination of polymers (such as hydroxypropyl methylcellulose 15 cps, sodium carboxymethyl cellulose and Carbopol 934p.) and ethyl cellulose as backing layer. The designed tablets were evaluated for various physical and biological parameters, drug content uniformity, *in-vitro* drug release, short-term stability, drug-excipients interactions (FTIR).

Results: The formulation HF_1 with the drug matrix layer composition- hydroxypropyl methylcellulose 15 cps (47% w/w), Carbopol 934p (3%w/w), and mannitol (channeling agent, 45% 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 (4.3 gm). Short-term stability studies 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.

Conclusion: The present study proves that buccoadhesive bilayer tablets of granisetron hydrochloride with controlled drug release properties can be successfully prepared by direct compression method using HPMC 15 cps and Carbopol 934p as mucoadhesive polymers and ethyl cellulose as backing layer.

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]. 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-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-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, its short half-life (3-4 h) and low molecular weight (348.9) make it suitable candidate for administration by buccal route. Hence, in the present study, an attempt was made to design and evaluate bilayer buccal tablets of GRN, with a view to overcome bioavailability problems, to reduce dose dependent side effects and frequency of administration.

MATERIALS AND METHODS: Granisetron hydrochloride was received as a gift sample from Cipla Pharma Ltd, Vikhroli, Mumbai. Sodium carboxymethyl cellulose (sodium CMC), hydroxypropyl methylcellulose 15 cps (HMPC 15 cps), Carbopol 934p, ethylcellulose (EC),

aspartame, magnesium stearate and D-mannitol were procured from SD Fine Chem., Mumbai.

Preparation of buccal tablets: Direct compression method has been employed [8] to prepare buccal tablets of GRN using sodium CMC, HMPC 15 cps and Carbopol 934 p 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 lubricant 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.**

TABLE 1: COMPOSITION OF BUCCOADHESIVE TABLETS

Ingredients*	Formulation Code					
	SCF_0	SCF_1	SCF_2	HF_0	HF_1	HF_2
Granisetron hydrochloride	1	1	1	1	1	1
Sodium CMC	50	47	44	---	---	---
HPMC 15 cps	---	---	---	50	47	44
Carbopol 934 p	---	3	6	---	3	6
D-mannitol	45	45	45	45	45	45
Aspartame	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2
Ethyl cellulose	50	50	50	50	50	50
Total weight	**150**	**150**	**150**	**150**	**150**	**150**

*Weights expressed as mg per tablet; HPMC- hydroxypropyl methylcellulose; sodium CMC- sodium carboxymethyl cellulose

Evaluation of buccal tablets: Twenty tablets were selected at random and weighed individually. The individual weights were compared with the 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, ten tablets were weighed and powdered. The powder equivalent to 1 mg of drug was extracted in to distilled water, filtered through 0.45 µm 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 1ml of distilled water (pH 6.8$\pm$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 [9] 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 $\pm$ 1^{o}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). The swelling index is calculated using the formula:

$$\text{Swelling index} = 100\ (w_2 - w_1) / w_1$$

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. This parameter for the tablets was measured on a modified physical balance [10-13] using bovine cheek pouch as model mucosal membrane (**Fig. 1**).

FIGURE 1: BIOADHESION TESTING APPARATUS

***In vitro* Drug Release Study [10]:** This was 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 by means of a syringe fitted with pre-filter and immediately replaced with fresh medium. The samples were filtered through 0.45 µm 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.

Stability Studies: Short- term stability studies were performed at a temperature of 40 ± 2° C / 75 ± 5% RH over a period of three months on the promising buccal tablet of granisteron hydrochloride (formulation HF_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 one month, the tablets were visually examined for any physical changes, changes in drug content and at the end of 3 month 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 buccoadhesive bilayer tablets of granisetron hydrochloride, 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 buccoadhesive bilayer 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.

The appearance of buccoadhesive tablets was smooth and uniform on physical examination. The hardness of prepared tablets of GRN was found 3.2 to 4.7 kg/cm^2; hardness increases with increasing Carbopol 934p proportion in the formulation. The thickness and

weight variation were found to be uniform as indicated by the low values of standard deviation, and were found to be in the range of 2.00 to 2.15 mm and 148 to 151 mg respectively. Friability values less than 1% indicate good mechanical strength to withstand the rigors of handling and transportation. Results are given in **Table 2**. The drug content of tablets was quite uniform as seen in the above mentioned table.

The average drug content of the tablets was found to be within the range of 93.86 to 96.56 % and the low values of standard deviation and coefficient of variation (< 2, not shown in the table) indicate uniform distribution of the drug within the prepared buccoadhesive 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 5.79 to 6.68. 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 behaviour. 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 Carbopol 934p increases the swelling index increases. The mucoadhesive strength of the tablets was found to be maximum in case of formulation SCF_2 i.e. 4.81 gm. This may be due to fact that positive charges on surface of Carbopol 934p could give rise to strong electrostatic interaction with mucous or negatively charged mucus membrane.

TABLE 2: EVALUATION OF BUCCAL TABLETS

Formulation code	Mean Hardness* (kg/cm2)	Mean Thickness* (mm)	Weight Variation* (mg)	Friability (%)	Mean % Drug Content*	Surface PH*	Swelling Index* (AFTER 8 h)	Mucoadesive Strength* (gm)
SCF0	3.2 (0.70)	2.10 (0.05)	149 (0.25)	0.72 (0.03)	93.86 (1.46)	6.68 (0.17)	17.36 (2.30)	4.00 (0.10)
SCF1	4.2 (0.91)	2.00 (0.04)	151 (0.40)	0.79 (0.02)	95.69 (0.89)	6.02 (0.23)	41.20 (1.90)	4.40 (0.120)
SCF2	4.2 (1.00)	2.00 (0.06)	149 (0.10)	0.80 (0.07)	94.67 (1.10)	6.08 (0.14)	52.70 (1.75)	4.81 (0.08)
HF0	3.7 (0.76)	2.15 (0.08)	150 (0.20)	0.69 (0.04)	95.45 (0.97)	6.48 (0.18)	21.38 (2.00)	3.90 (0.10)
HF1	4.5 (0.90)	2.00 (0.05)	148 (0.25)	0.74 (0.05)	96.56 (0.67)	5.79 (0.12)	37.80 (1.80)	4.30 (0.12)
HF2	4.7 (0.81)	2.05 (0.10)	151 (0.40)	0.78 (0.06)	96.23 (1.28)	5.97 (0.10)	49.30 (1.50)	4.70 (0.10)

*Average of three determinations, values shown in parenthesis are standard deviations. Formulation HF_1 was selected as the best and used for further studies

***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 200ml of pH 6.8 phosphate buffer as dissolution medium. From dissolution data it is evident that the designed formulations have displayed more than 88% drug release in 8 h. The formulation HF_1 with the drug matrix layer composition- HPMC 15 cps (47% w/w), Carbopol 934p (3%w/w) and mannitol (channeling agent, 45% w/w) was found to be promising, which showed $t_{50\%}$, $t_{70\%}$ and $t_{90\%}$ values of 2.83, 4.60 and 7.30 h respectively and released 94% drug within 8 h. Results are shown in **Table 3** and the drug release profiles depicted in **figures 2** and **3**. A comparison of the release parameters is shown in **figure 4**.

TABLE 3: *IN VITRO* DRUG RELEASE PARAMETERS

FORMULATION CODE	$t_{50\%}$ (h)	$t_{70\%}$ (h)	$t_{90\%}$ (h)	CUMULATIVE % DRUG RELEASE IN 8 h *±SD
SCF_0	2.60	4.65	7.25	95.45±0.76
SCF_1	3.10	5.10	7.78	91.91±1.57
SCF_2	3.75	5.65	>8.00	88.12±1.57
HF_0	2.42	3.62	6.15	98.23±0.44
HF_1	2.83	4.60	7.30	93.92±0.44
HF_2	3.05	5.00	8.00	90.14±0.76

$t_{50\%}$, $t_{70\%}$ and $t_{90\%}$ are time for 50%, 70% and 90% drug release respectively; *Average of three determinations, SD-standard deviation

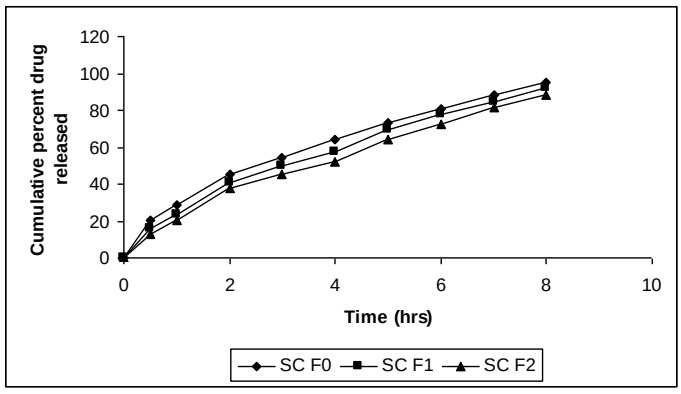

FIG. 2: *IN VITRO* DRUG RELEASE PROFILES OF FORMULATIONS USING SODIUM CMC AS MUCOADHESIVE POLYMER

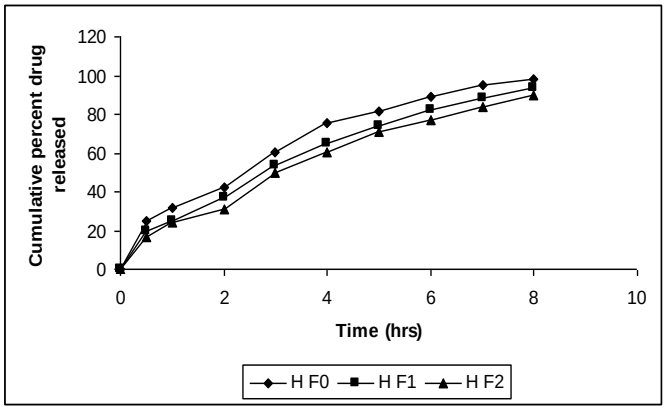

FIG. 3: *IN VITRO* DRUG RELEASE PROFILES OF FORMULATIONS USING HPMC (15 cps) AS MUCOADHESIVE POLYMER

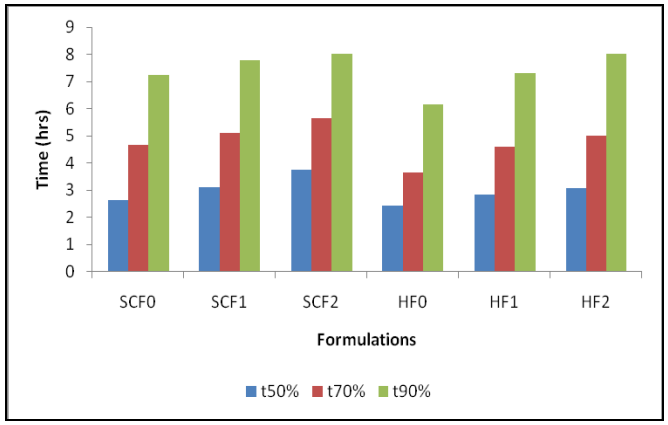

FIG. 4: COMPARISON OF DISSOLUTION PARAMETERS ($t_{50\%}$, $t_{70\%}$ AND $t_{90\%}$) OF BUCCOADHESIVE TABLETS OF GRANISETRON HYDROCHLORIDE

Drug Release Kinetics: *In vitro* drug release data of all the buccoadhesive 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 (after an initial burst release of 15-20% drug, with 'r' values from 0.9634 to 0.9877). Higuchi and Peppas data reveals that the drug is released by non-Fickian diffusion mechanism ('r' values from 0.9881 to 0.9948 and 'n' values from 0.680 to 0.811). 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 HF_1 (peaks at 3288, 1638 and 1540 cm^{-1} due to -NH, C=O and -CN stretching respectively). The presence of above peaks confirms undisturbed structure of drug in the above formulation. Hence, there are no drug-excipients interactions. From the stability studies data indicates that the drug content of formulation HF_1 was not significantly affected at 40 ± 2° C / 75 ± 5% RH after storage for three months. Statistical analysis of the drug content data (by student 't' test) gives 't' value of 2.94 which is much less compared to the table value of 4.3 ($p<0.05$).

CONCLUSIONS: The results of the present study indicate that buccoadhesive bilayer tablets of GRN with controlled drug release can be successfully prepared by direct compression method using HPMC 15 cps and Carbopol 934p as mucoadhesive polymers and ethyl cellulose as backing layer. The formulation HF_1 with the drug matrix layer composition- HPMC 15 cps (47% w/w), Carbopol 934p (3%w/w) and mannitol (channeling agent, 45% w/w) was found to be promising, which shows an *in vitro* drug release of 94% in 8 h along with satisfactory bioadhesion strength (4.3 gm).

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REFERENCES:

1. Langer MA, Robinson RJ. Sustained release drug delivery systems In: Remington's Pharmaceutical Sciences, Gennaro AR (Ed.), New York: Mack Publishing Company; seventeenth edition 1985; p.1644-61.

2. Vyas SP, Khar KR (Eds). Controlled drug delivery concepts and advances, NewDelhi: Vallabh Prakashan; first edition 2002; p. 292.

3. Tripathi KD. 5-hydroxytryptamine and their antagonists. In: Essentials of Medical Pharmacology, Delhi: Jaypee Brothers Publishers (P) Ltd; fourth edition 1999; p. 189-190.

4. Laurence LB, John SL, Keith LP (Eds). Goodman and Gilman's The Pharmacologic Basis of Therapeutics. New York: McGraw Hill Publishing Company; eleventh edition 2006; p.1000-3.

5. Linda S, Crawford SM, Taylor PA. The comparative effectiveness of ondansetron and granisetron in once daily dosage in the prevention of nausea and vomiting caused by cisplatin: a double blind clinical trial. The Pharm J 2000; 265, (7104): 59-62.

6. Sweetman SC (Ed). Martindale: The Complete Drug Reference, London: Pharmaceutical Press; thirty third edition 2002; p.1127-8.

7. Paul Beringer (Ed). Remington's Science and Practice of Pharmacy, Baltimore, Maryland (USA): Lippincott Williams and Wilkins Publishing Company; twenty first edition 2005; p.1311.

8. Prasad BK, Remeth JD, Kailas KM, Vijay DH, Niranjan SM .Formulation and evaluation of buccoadhesive tablets of atenolol. J Pharm Res 2008; 1 (2): 193-9.

9. Ramana MV, Nagda C, Himaja M. Design and evaluation of mucoadhesive buccal drug delivery systems containing metoprolol tartrate. Indian J Pharm Sci 2007; 69(4): 515-8.

10. Patel MV, Prajapati GB, Patel VH, Patel MK. Mucoadhesive bilayer tablets of propranolol hydrochloride. AAPS PharmSciTech 2007; 8(3), Article 77: E1-E6.

11. Swamy P.V, Pawandeep Singh, Hiremath SN, Shirsand SB, Neelima and Raju SA. Preparation and evaluation of chitosan buccal films of diltiazem hydrochloride. Indian Drugs 2007; 44(2): 137-9.

12. Ahuja A, Dogra M Agarwal SP, Development of buccal tablet of diltiazem hydrochloride. Indian J Pharm Sci 1995; 57(1): 26-30

13. Gupta A, Garg S, Khar LK. Measurement of bioadhesive strength of mucoadhesive buccal tablets: design of an *in vitro* assembly. Indian drugs 1993; 30 (4): 152-5.