Asian Journal of Pharmaceutical Technology & Innovation
ISSN: 2347-8810

Research Article

Received on: 31-08-2015
Accepted on: 07-09-2015
Published on: 15-10-2015

Corresponding Author

***Harish Goyal,**

Research Scholar,
Department of Pharmaceutics, Lloyd Institute of Management and Technology,
Knowledge Park 2, plot no # 11, Greater Noida U.P, India.
Mob. no.: 08802725115

Email:harishgoyal2000@gmail.com

Formulation and Evaluation of BuccalFilms of Ranitidine Hydrochloride

Harish Goyal*, Sameer Rastogi, Vandana Arora, Vijay Bhalla

ABSTRACT

Buccal drug delivery system is been considered as a potential non invasive route of drug administration with several advantages viz prolonged therapeutic effect dose reduction improved bioavailability lesser side effects than conventional dosage forms etc. The present investigation involves formulation evaluation and comparison of formulated polymeric buccal patches using ranitidine HCL as model drug the formulations were prepared by solvent evaporation / casting method. The prepared buccal patches were evaluated for thickness, drug content uniformity, weight variation, folding endurance, swelling index, surface pH, surface morphology, in-vitro & ex-vitro drug release.*In-vitro* release studies were performed across cellophane membrane using Franz Diffusion Cell (FDC). The surface morphology of the patch was examined by Scanning Electron microscopy (SEM). Based on the physicochemical and *in-vitro* release study, formulation F3, F4 and F5 were chosen for further *ex-vivo* release studied. *Ex- vivo* permeation studied were carried out through buccal mucosa of pig using FDC. Drug release data were fitted to various pharmacokinetic model equations such as zero order kinetics, first order kinetics, Higuchi's and korsmeyerPeppas model in order to find out mechanism of drug release.

Key-words: Ranitidine, Buccal Patches, Mucoadhesives, Antiulcer

Cite this article as:
Harish Goyal, Vandana Arora, Vijay Bhalla, Formulation and Evaluation of Buccal Films of Ranitidine Hydrochloride, Asian Journal of Pharmaceutical Technology & Innovation, 03 (14); 2015. www.asianpharmtech.com*

Introduction

Buccal drug delivery system is been considered as a potential non invasive route of drug administration with several advantages viz prolonged therapeutic effect dose reduction improved bioavailability lesser side effects than conventional dosage forms etc.[1]Ranitidine HCI is a competitive inhibitor of histamine H2 –receptors resulting in the inhibition of gastric acid secretion and an effective alternative in the treatment of duodenal and peptic ulcers pathological hypersecretory conditions (such as zollinger – Ellison syndrome)gastroesophageal reflux disease [GERD]erosive esophagitis and maintenance of healing of erosive esophagitis the bioavailability of ranitidine HCI following oral administration is about 50 % which might be due to colonic degradation by colonic bacteria the bioavailability of ranitidine HCI is markedly lower from the human colon than the upper part of gastro intestinal tract.[2-3]

In the present context the buccal route ranks with oral treatment s the successful innovate research area in the drug delivery.It has been found that oral controlled release dosage forms are not suitable for variety of important drugs characterized by the incomplete availability of drug in systemic circulation. However the success of a drug to be used for systemic delivery via buccal route depends mainly on the ability of the drug to permeate through buccal mucosa in sufficient quantities which can be achieved with the help of penetration enhancers. Thus, the role of penetration enhancers comes to play. They act on polar and non-polar molecules by altering the multilamellate pathway for penetration and even increase drug diffusivity through mucous membrane proteins. Hence, penetration enhancers have a very significant impact on the design and development of an effective product. Ranitidine HCI is the preferred drug because it has plasma half life of 3-4hrs and has low bioavailability which is an essential condition for formulation of buccal patches. Moreover, sustained release of drug in certain situations may be desirable to improve the bioavailability and the therapeutic efficiency of the drugs. In the study, hydrophilic polymers like Carbopol-934k (CP-934k) &Carboxymethyl Cellulose Sodium salt (SCMC) were used in different concentrations.

MATERIALS AND METHODS

Ranitidine, Hydroxy propyl methyl cellulose-15 cps, Poly vinyl pyrrolidone was procured from Drugs India, Hyderabad, India. Ethanol (O.R Distilleries, Renigunta, India), Dichloromethane (Universal laboratories pvt ltd, Mumbai, India), Propylene glycol (Karnataka fine chem. industries, Bangalore, India). All other chemicals were of analytical grade and procured from S.D fine chemicals, Mumbai, India. The films were prepared by solvent casting method. Concentrations of ranitidine were measured with UV-VIS Spectrometer Labomed, Inc, USA. (Model No: 2602).

Fabrication of Ranitidine Buccal Films

The films were prepared by the method of solvent casting technique6-8 employing 'O' shape ring placed on a glass surface as substrate. Composition of a single circular cast film of various formulations is given in the Table.1. The calculated quantities of polymers Hydroxy Propyl Methyl Cellulose - 15 cps (HPMC) and Poly Vinyl Pyrrolidone (PVP) were dispersed in ethanol and dichloromethane. An accurately weighed 100 mg Ranitidine was incorporated in polymeric solutions after levigation with 30 % w/w propylene glycol which served the purpose of plasticizer as well as penetration enhancer. The solution was mixed occasionally to get semisolid consistency. Then this were casted on a glass surface employing 'O' shape ring having 4.2 cm in diameter is covered with funnel to controlling the evaporation of solvent and allowed to dry at room temperature over night. The dried films were separated and the backing membrane used was aluminium foil. Then the formulations were stored in a desiccator until further use.[4-6]

Surface pH of films

Buccal patches were left to swell for 2 h on the surface of an agar plate, prepared by dissolving 2 % (w/v) agar in warmed isotonic phosphate buffer of pH 6.8 under stirring and then pouring the solution into a petridish till gelling at room temperature. The surface pH9 was measured by means of a pH paper placed on the surface of the swollen patch. The mean of three reading was recorded.

Percentage moisture absorption (PMA)

The percentage moisture absorption10 test was carried out to check the physical stability of the buccal films at high humid conditions. In the present study the moisture absorption capacity of the films were determined as follows. Three 1cm diameter films were cut out and weighed accurately then the films were placed in

desiccator containing saturated solution of aluminium chloride, keeping the humidity inside the desiccator at 79.5 %. After 3 days the films were removed, weighed and percentage moisture absorption was calculated. Average percentage moisture absorption of three films was found.

Percentage moisture absorption = Final weight – Initial weight X 100
Initial weight

Percentage moisture loss (PML)

Percentage moisture loss10 was also carried to check the integrity of films at dry condition. Three 1cm diameter films was cut out and weighed accurately and kept in desiccator's containing fused anhydrous calcium chloride. After 72 hours the films were removed, weighed. Average percentage moisture loss of three films was found out.

Percentage moisture loss = Initial weight – Final weight X 100
Initial weight

Swelling Percentage (% S)

A drug loaded films were placed in a thoroughly cleaned petridish and a graph paper was placed beneath the petridish, to measure the increase in area due to swelling of the film. Fifty ml of pH 6.8 phosphate buffer was poured into the petridish. An increase in the weight of the
patch was noted in 15 min intervals for 60 min and the weight was calculated. The swelling percentage11,12 was calculated by using the following formula,

$$\% S = \frac{Xt - X_0}{X_0} \times 100$$

Where, % S - swelling percentage, Xt - the weight ofswollen film after time t, X0 -weight of film at zero timezero.

Water vapour transmission rate (WVT)

For water vapour transmission rate13 study vials of equal diameter were used as transmission cells. These cells were washed thoroughly and dried in an oven. About 1 g of calcium chloride was taken in the cell and the polymeric films measuring 2 cm2 area were fixed over
the brim with the help of an adhesive. The cells were weighed accurately and initial weight was recorded, and then kept in a closed desiccators containing saturated solution of potassium chloride. The humidity inside the desiccators was found in between 80 – 90 % RH. The cells were taken out and weighed after 18, 36, 54 and 72 hrs. From increase in weights the amount of water vapour transmitted and the rate at which water vapour transmitted were calculated by using the following formula.

$$W V T = WL/S$$

Where, W is water vapour transmitted in mg, L is thickness of the film in mm, S is exposed surface area in cm2.

Film weight and thickness

For evaluation of film weight three films of every formulation were taken and weighed individually on a digital balance (ESSAE, Goa, DS-852J). The average weights were calculated, similarly, three films of each formulation were taken and the films thickness was measured using Digital verniercaliper (Absolute Digimate) at six different places and the mean value was calculated.

Folding endurance

Folding endurance14 of the film was determined by repeatedly folding one patch at the same place till it broke or folded manually, which was considered satisfactory to reveal good film properties. The number of times of film could be folded at the same place without breaking gave the value of the folding endurance. This test was done for three films.

Drug content uniformity

A film was cut into three peaces of equal diameter were taken in separate 100 ml of pH 6.8 phosphate buffer was added and continuously stirred for 24 h. The solutions were filtered, suitably diluted and analyzed at 313 nm in a UV Spectro meter. The average of drug content of three films was taken as final reading.

***In vitro* release study**

The drug release studies were performed with USP dissolution test apparatus8. (Paddle method). The USP dissolution apparatus was thermostated at the temperature of 37±1o C and stirred at rate of 50 rpm. Each film was fixed on a glass slide with the help of cyanoacrylate adhesive so that the drug could be release only from upper face. Then the slide has immersed in the vessel containing 500 ml of pH 6.8 phosphate buffer solution.
The aliquots of 1 ml were withdrawn at the time interval of every hour and replaced with equal volume of dissolution medium. The sink condition was maintained throughout the study. The samples were analyzed at 313 nm in a UV-VIS Spectrometer and cumulative amount of drug release at various time intervals was calculated.[7-12]

Result and Discussion:

Buccal films of Ranitidine were prepared by the method of solvent casting technique employing 'O' shape ring having diameter of 4.2 cm placed on a glass surface as substrate with mucoadhesive polymers of HPMC 15 cps and PVP. Ethanol and Dichloromethane is used as thesolvents. Propylene glycol was used as the plasticizer as well as penetration enhancer. The drug delivery system was formulated as a matrix controlled drug delivery. The prepared ranitidine buccal films were evaluated or characterized based upon their physico chemical characteristics like surface pH, PMA, PML, swelling percentage, WVT, thickness, weight, folding enduranceand drug content.
Matrix system based Buccal patches of Ranitidine HCI were prepared using different proportions of NaCMC and CP-934k as matrix/film formers and glycerol as both plasticizer and penetration enhancer. The result of present investigation stated that Sod. Carboxymethyl cellulose and Carbopol 934k have good matrix/film forming characteristics which was confirmed by the visual and physiological characterization of the patches. The in-vitro and ex-vivo studies indicate that successful buccal patches of Ranitidine HCI could be prepared using hydrophilic polymers viz. NaCMC and CP-934k employing solvent casting technique. It was found during investigation that as the concentration of Sod. Carboxymethyl Cellulose was increased the release rate also inclined and the patches showed lesser mucoadhesion time while on the other hand as the concentration of Carbopol 934k was increased the drug release was found to be controlled and the patch also reflected sufficient mucoadhesion time period. Although, a very slight correlation was found between the formulations selected after in-vitro release studies and were studied for ex-vivo permeation studies. Out of the three selected formulations (i.e. F3, F4 & F5), the formulation F5 showed the best permeation release All the necessary and important physiochemical properties, for development of effective and efficient dosage form of Ranitidine HCI were studied.

Physical Characterization of Drug

Ranitidine HCI was evaluated for its physical properties and it was observed that it is a yellow free flowing crystalline powder with no odor and bitter taste. The physical properties were found similar to that reported in literature.

Solubility

The solubility of Ranitidine HCI was observed visually which shows the drug is soluble in polar solvents while insoluble or very slightly soluble in non-polar solvents.

Melting Point Determination

The melting point of drug was found to be 144^{0}C, which corresponds to the literature value of 136 to 145^{0}C and proves the identity and purity of drug.

UV-Spectrophotometric Study

UV-Spectrophotometric study was carried out in order to determine the λ_{max} of Ranitidine HCI in PB Ph6.8. The test medium when scanned for absorption maxima in triplicate ranging from 200-400 nm was found to be as in Table 1 shows the peak at 312.8 nm of Ranitidine HCI in pH6.

Table.1: Scanned λ_{max} and absorbance value of sample of Ranitidine HCI prepared in PB(pH6.8)(in triplicate).

Day	Strength (µg/ml)	Scanned λ_{max}	Absorbance
1	10	312.8	0.443
2	10	312.8	0.448
3	10	312.8	0.443

The scanned λ_{max} were found to be similar as that of reported λ_{max}(313 nm).

Drug Excipient Interaction Study:

Fourier Transform Infrared Spectroscopy (FTIR) Analysis:

The infrared spectra were obtained using a scale of wave numbers (cm-1). The IR spectra`s of mixture of polymers (NaCMC and CP 934k), drug (Ranitidine HCI) and mixture of drug and polymer were shown.

IR spectral analysis of Ranitidine HCI alone showed that the principal peaks were observed at wave numbers at 3325-3050cm^{-1}(N-H), free-NH at 3270-3200cm^{-1} and dimethylamino groups give bands at 2828-2780 cm-13319.86 cm^{-1}(secondary amine), 2937.06 cm^{-1}(C-H group stretching vibration). In the IR spectra of the physical mixture of Ranitidine HCI, CP934k and NaCMC, the major peaks of Ranitidine HCI were observed at 3250-3100, 2600, 1600-1400, 1455, 1318, 524-380 cm^{-1}. Thus it was observed that there were no changes in the main peaks in IR spectra of mixture of drug and polymers as compared to the spectra of pure drug, indicating no significant interaction between drug and polymers.

Digital Scanning Calorimetry (DSC) analysis:

The DSC thermograms of samples pure drug, CP 934k and NaCMC were recorded on a DSC (PerkinElmer Thermal Analysis). The samples were heated in hermetically sealed aluminium pans over a temp range 50-500^{0}C at a constant rate of 50c/min under N_2 purge (20ml/min).

Table 2: Results of DSC analysis.

S.NO	Specimen	Reported ()	Experimental ()
1	Ranitidine HCL	136-145	144.29
2	Carbopol 934k	100-120	133
3	Sod. Carboxymethyl cellulose	300	332

The peak at 144.29°C i.e the melting point of drug was disappeared in the thermogram of the formulation which may be indicating the uniform distribution of the drug within the polymer matrix.

Evaluation of Buccal Patches:

Physicochemical Evaluation of Buccal Patches:

The prepared buccal patches were evaluated for their physicochemical characteristics such as weight variation, thickness, folding endurance, drug content. The physicochemical characteristics are summarized as follows;

Table 3: Results of various evaluation parameters.

Formulation Code	Thickness (mm)	Weight Variation (mg)	Folding Endurance	Drug Content (mg)	Mucoadhesion Time	% Elongation at Break
F1	0.09 ± .013	45.4±0.24	>300	29.1±.26	9H:50min±0.43	75%±0.055
F2	0.085±.005	44.8±0.32	>300	29.6±.19	11h:30±0.60	55%±0.065
F3	0.12±.005	46.1±0.29	>300	28.7±.16	9h:10min±0.35	90%±0.076
F4	0.10±.015	44.9±0.38	>300	29.5±.25	8h:20min±0.40	110%±0.076
F5	0.095±.013	45.3±0.19	>300	28.9±.12	8h:40min±0.55	45%±0.076

Weight variation:

The weights ranged between 44.8±0.32 to 46.1± 0.29, which indicate that all the formulations exhibited uniform weight with standard deviation values indicating the uniformity of the patches.

Thickness:

The thickness of the patches varied from 0.085±.005 to 0.12±.005.Low standard deviation values in the film thickness measurements ensured uniformity of the patches prepared by solvent casting technique.

Folding endurance:
The folding endurance value can be defined as `the number of times a film can be folded at the same place without breaking`. This test is an index of the brittleness of the film; the lower the folding endurance value, the more brittle the film. It is an important test to assess the integrity of the film. The films tolerated more than 300 folding (n = 5), and were found to be more elegant, smooth, transparent and flexible, properties which can be attributed to the plasticizer.

%Elongation At break:
The % elongation at break value varies from 145% ± 0.076 to 210% ± 0.028 which shows the prepared patches possessed goog tensile strength.

Surface pH:
Patches of different compositions were taken on separate glass slides and wetted very slightly by distilled water with the help of a syringe needle. The calibrated glass electrode brought near the surface of the patches in such a manner so as to just touch the patch surface and the readings were noted. The resulted pH of all fabricated patches was found to be near around 6.0.

Drug content:
Drug content from all the formulations was determined in phosphate buffer pH 6.8. Good uniformity of drug content the batches was observed with all formulations and ranged from 28.7 ± .06 to 29.6 ± .09 mg. The results indicate that the process employed to prepare patches in this study was capable of producing patches with uniform drug content and minimal patch variability.

%Swelling Index:
Patches of area 1cm^{2}were retrieved from the film and weighed using electronic weighing balance and then were soaked in distilled water for 3-4 hours in a petridish. After given time the patches were taken out from petridish and excess water was removed with the help of filter paper. The swelled patches were weighed again on the same balance and the increases in weight were noted. Swelling index was calculated using the formula mentioned in its respective section and results are as follows:

Table .4: % Swelling index of patch formulations F1-F5.

Formulation code	Initial Code	Final Weight	% Swelling index
F1	45.5±0.24	60.4±0.70	24.67
F2	44.4±0.32	64.1±1.65	30.73
F3	45.1±0.29	59.4±2.55	24.07
F4	45.9±0.38	60.7±2.99	24.38
F5	46.3±0.19	63.9±2.17	27.54

Scanning Electron Microscopy
Homogeneous distribution of the drug throughout the matrix is one of the important criteria to get the reproducible release rate from a definite area of patch on application. It can be ascertained by Scanning Electron Microscopy (SEM). The surface morphology of the patches was studied for drug loaded and placebo patches. The SEM
Photograph of the placebo patch was shown in figure 1 and SEM photograph of drug loaded patch showed that the drug is dispersed throughout the matrix patch.

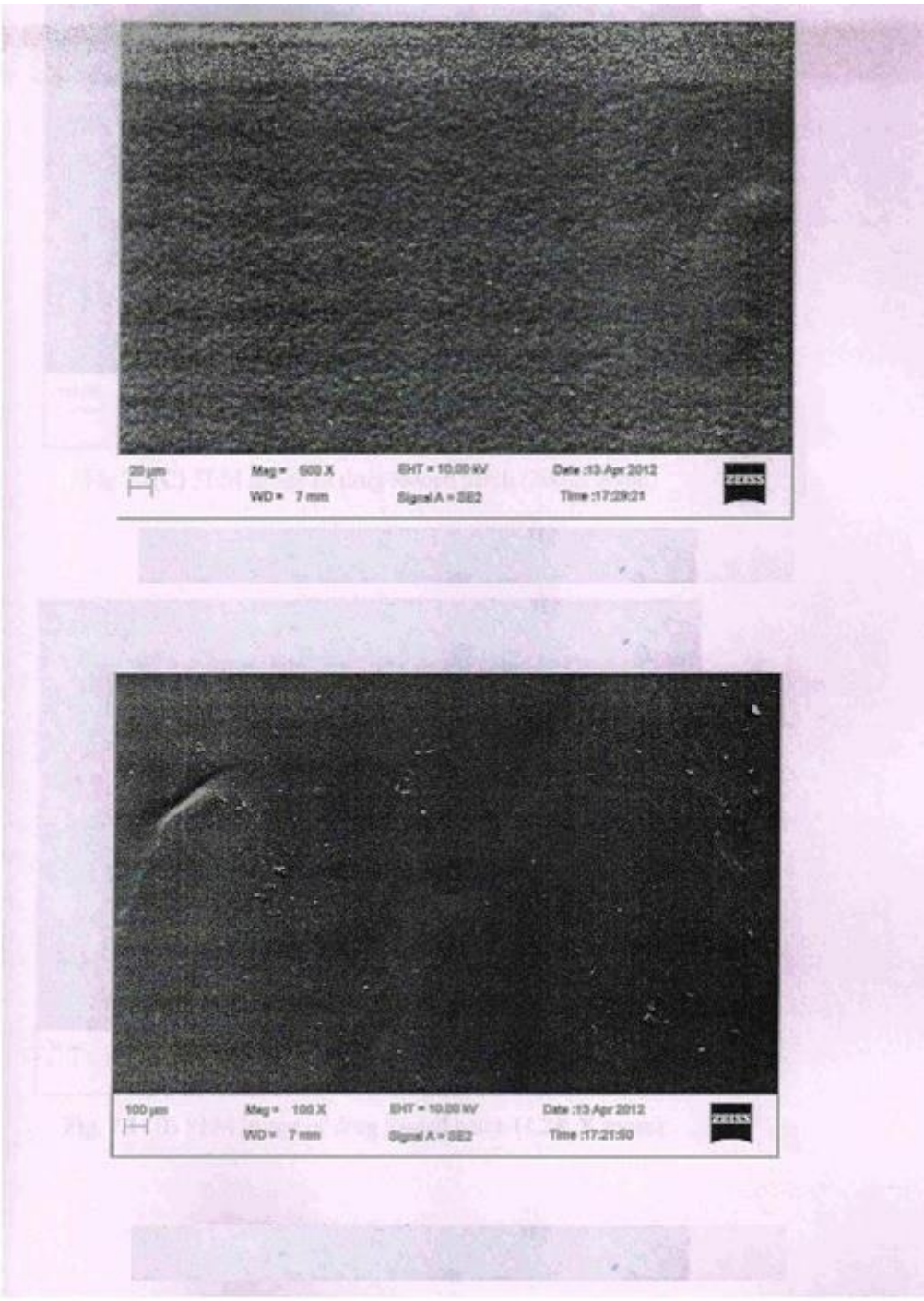

Figure 1: SEM image of blank and loaded patches(100X zoom)

Conclusion

In conclusion the present data indicate a confirm reproducibility of developing Ranitidine HCI Buccal Patches that could be used for treating several predicaments. The drug release was found to be sustained and prolonged and thus, multiple dose regimes could be best replaced by single buccal formulation. Further study in respect to in-vivo performance after application of buccal patch is required to substantiate the therapeutic efficiency of these systems.

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