ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 8, Issue 3, 2015

ISSN - 0974-2441

Research Article

FORMULATION AND CHARACTERIZATION OF MUCOADHESIVE BUCCAL FILM OF RANITIDINE HYDROCHLORIDE USING STERCULIA FOETIDA GUM AS POLYMER

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Received: 9 August 2014, Revised and Accepted: 13 September 2014

ABSTRACT

The aim of the present study was to develop buccal drug delivery system of *Sterculia foetida* gum and Ranitidine HCl. Buccal film of Ranitidine HCl was developed using mucoadhesive polymer *S. foetida* gums like. The prepared films were evaluated in terms of their physical characteristics and *in vitro* release. The formulation was optimized for the different concentration of *S. foetida* gum. The results of *in vitro* release studies showed that optimized formulation (A4) could sustain drug release (98.79%) for 12 hrs. The release profiles were subjected to various kinetic equations like Higuchi diffusion equation and Peppas exponential equation. The regression coefficient values of this kinetic equation are very nearer to one suggesting that plots are fairly linear and slope values of the Peppas equation is (>1) suggest that drug was released by diffusion mechanism following non-Fickian transport. Mucoadhesive buccal films of Ranitidine HCL sustained release, and non-Fickian transport of the drug from film was confirmed.

Keywords: Ranitidine HCl, Buccal drug delivery system, *Sterculia foetida* gum, Sustaine release.

INTRODUCTION [1-5]

The real issue in the development of mucoadhesive sustain release dosage forms is not just to prolong the delivery of drugs for 12 hrs, but to prolong the presence of the dosage forms onto the mucus membrane until all the drug is released for the desired period of time. Rapid secretion of saliva could result in removal drug delivery device from the absorption zone leading to diminished efficacy of the administered dose. Several approaches are currently used to retain the dosage form in the buccal region. This includes mucoadhesive drug delivery system. The principle of mucoadhesion offers a simple and practical approach to achieve increased mucoadhesive residence time for the dosage form and sustained drug release. Ranitidine HCl is a H_2-receptor antagonist, often shortened to H_2 antagonist, is a drug used to block the action of histamine on parietal cells in the stomach, decreasing acid production by these cells. Nowadays natural gum are gaining importance as promising biodegradable polymeric materials. Many studies have been carried out in the field of pharmaceuticals using natural gums as polymers. The gums have many advantages over synthetic materials. Various applications of gums have been established in the field of pharmaceutical formulation of novel drug delivery systems, biotechnological applications, and other delivery systems. Therefore, in the years to come, there will be continued interest in natural gums and their modifications aimed at the development of better materials for drug delivery systems. In the present research work, we have attempted the formulation Ranitidine HCl buccal films by the use of natural polymer *Sterculia foetida* gum with an objective of improving bioavailability of the drug.

Drug polymer compatibility studies

The pure drug and physical mixture of drug and polymers were subjected to infrared (IR) spectroscopic study using FT-IR spectrophotometer (IR Affinity-1, Shimadzu). The spectra were scanned over the wave number range from 4000 to 400/cm.

MATERIALS AND METHODS

Materials

Ranitidine HCl was obtained as a gift sample from Vama Pharma, Nagpur. The Gum of *Sterculia foetida* (Sterculiaceae) was procured from the vendor Mr. Waghbrothers, Nagpur. The gum was authenticated and approved macroscopically and microscopically by Senior Taxonomist Dr. Vinayak Naik, Nicholas Piramal Mumbai. The above gum was used for research work. All other chemicals used in the study were of analytical grade.

Methods [6,7]

The composition of different formulations of Ranitidine HCl buccal films is shown in Table 1. The films were prepared by the method of solvent casting technique employing 'O' shape glass ring placed on a mercury surface in a petry plate. The calculated quantity of carbopol 934P was dispersed in water. An accurately weighed 100 mg Ranitidine HCl was incorporated in polymeric solutions after levigation with 30% w/w propylene glycol. To this polymeric solution, *S. foetida* gum was added. The solution was mixed continuously on the magnetic stirrer with heating to get semisolid consistency. The resulting solution was casted on a mercury surface employing 'O' shape ring and allowed to dry in oven. The dried films were cut into 1 cm diameter pieces and kept in desiccator till further use.

Evaluation of ranitidine HCl films [8-11]

The Ranitidine HCl buccal films were evaluated for the following properties.

Physical properties

a) Physical appearance and surface texture

The physical appearance was noted by the visual inspection of the films and surface texture was detected by touch.

Table 1: Formulation of SFG and Carbopol 934P buccal films containing Ranitidine HCl

Formulation code	Drug (mg)	SFG (mg)	Carbopol 934P (mg)	Propylene glycol (30% w/w)	Water (ml)
A1	100	200	10	2 ml	13
A2	100	200	20	2 ml	13
A3	100	200	40	2 ml	13
A4	100	200	60	2 ml	13
A5	100	200	80	2 ml	13
A6	100	200	100	2 ml	13
A7	100	200	-	2 ml	13
A8	100	-	200	0.5 ml	14.5

b) Weight uniformity of films

For weight uniformity determination, three films of the size 10 mm diameter were weighed individually using a digital balance and the average weight was calculated.

c) Thickness of films

Thickness of the films was measured using digital vernier caliper. The thickness was measured at three different sites of the films and average was taken.

d) Swelling index of films

The swelling index of the films was determined by immersing preweighed film of size 10 mm in 25 ml distilled water. The films were taken out carefully at 5, 10 up to 30 minutes. intervals, blotted with filter paper and weighed accurately.

The swelling index was calculated by the formula,

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

e) Surface pH of films

Surface pH of the films was determined by bringing a combined glass electrode or pH paper near the surface of films previously wetted with distilled water and allowing the equilibration for 1 minute.

f) Percent moisture absorbance

The percentage moisture absorption (PMA) test was carried out to check the physical stability of the buccal films at high humid conditions. Three 1 cm diameter films were cut out and weighed accurately. Then the films were placed in a desiccator containing a saturated solution of aluminum chloride, keeping the humidity inside the desiccator at 75%. After 3 days, the films were removed, weighed, and PMA was calculated. Average PMA of three films was calculated.

$$\text{Moisture absorbance} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Final weight}} \times 100$$

g) Percentage moisture loss (PML)

PML was carried to check the integrity of films at dry condition. Three 1cm diameter films were cut out and weighed accurately and kept in desiccator containing fused anhydrous calcium chloride. After 3 days, the films were removed, weighed. Average PML of three films was calculated.

$$\%\ \text{Moisture loss} \frac{\text{Final weight} - \text{Initial weight}}{\text{Final weight}} \times 100$$

h) Folding endurance of films

The flexibility of films can be measured quantitatively in terms of folding endurance. Folding endurance of the films was determined by repeatedly folding (10 mm) films at the same place till it was broken. The number of times films could be folded at the same place without breaking gave the value of folding endurance.

i) Mucoadhesive strength

Mucoadhesive strength of the film was measured on a modified physical balance. The fresh sheep buccal mucosa was cut into pieces and washed with phosphate buffer (pH 6.8). A piece of buccal mucosa was tied to the open mouth of a glass vial, which was filled completely with phosphate buffer (pH 6.8). The glass vial was placed and tightly fitted in the center of glass beaker. The phosphate buffer (pH 6.8, 37±10°C) was filled in the glass beaker just touching the mucosal surface. The film was stuck to the lower side of rubber stopper with cyanoacrylate adhesive. Two pans of the balance were balanced with 5 g weight on the right-hand side pan. A weight of 5 g was removed from the right-hand side pan, which lowered the pan along with the film over the mucosa. The balance was kept in this position for 5 minutes contact time. The water (equivalent to weight) was added slowly with infusion set (100 drops/minutes.) to the right-hand side pan until the film detached from the mucosal surface. The weight in grams required to detach the film from the mucosal surfaces gave the measure of mucoadhesive strength.

j) Drug content uniformity study of films

The films were tested for drug content uniformity by UV-spectrophotometric method. Films of size 10 mm diameter were cut from three different places from the casted films. Each film was placed in 100 ml volumetric flask and dissolved in phosphate buffer (pH 6.8), and 0.2 ml was taken and diluted with phosphate buffer (pH 6.8) up to 10 ml. The absorbance of the solution was measured at 313 nm using UV spectrophotometer. The percentage drug content was determined using the standard graph and the same procedure was repeated for three films.

***In-vitro* drug release of films [12]**

In-vitro, drug release studies were carried out by attaching buccal mucosa to one end of the Franz diffusion cell which acted as donor compartment. The buccal films containing drug was placed inside donor compartment which is agitated continuously using a magnetic stirrer and then temperature was maintained at 37±1°C. The receptor compartment consisted of 100 ml of phosphate buffer (pH 6.8). 2 ml sample was withdrawn at periodic intervals from the receptor compartment and replaced with fresh phosphate buffer (pH 6.8) immediately. The drug release was analyzed spectrophotometrically at 313 nm. The results are shown in Table 15.

Stability studies [13]

To assess the drug and formulation stability, stability studies were done as per ICH guidelines. The formulated buccal films were wrapped in aluminum foil and stored at 25±0.5°C and 45±0.5°C for period of 1 month. After an interval of 15 days, the films were tested for physical appearance, weight variation, thickness and drug content uniformity.

RESULTS AND DISCUSSION

Buccal films of ranitidine HCl were prepared by the method of solvent casting technique employing 'O' shape ring having diameter of 4.2 cm placed on a mercury surface as substrate with mucoadhesive polymers *S. foetida* gum and carbopol 934P. Water is used as the solvents. Propylene glycol was used as the plasticizer. The prepared Ranitidine HCl buccal films were evaluated or characterized based upon their physicochemical characteristics like surface pH, PMA, PML, swelling percentage, water vapour transmission, thickness, weight, folding endurance and drug content. These results are shown in Table 2. The *in vitro* drug release study was performed using Franz Diffusion cell and was thermostated at 37±1°C.

Physical appearance and surface texture were checked by visual inspection of films and feel or touch. The observations revealed that the films were yellow in color having smooth surface and elegant in appearance.

The weight of the films was determined using digital balance and the average weight of all films is given in Table 2. The drug loaded films were tested for uniformity of weight. The films were found to be uniform in weight. The average weight of the films of *S. foetida* in combination with carbopol 934 (A1-A6) was found about 29.13±1.17, 30.90±1.31, 31.46±1.13, 32.20±1.17, 33.26±1.34 and 33.9±1.14 mg respectively. The films prepared with *S. foetida* alone (A7) weighed about 27.66±1.24 mg whereas the films prepared with carbopol 934 alone (A8) was weighed about 27.23±1.27 mg. In all the cases, the calculated standard deviation values are very low which suggest that the prepared films are uniform in weight.

The thickness of the films is measured using digital vernier caliper, and the average thickness of all films is given in Table 2. The drug loaded films were tested for uniformity of thickness. The films were found to be uniform in thickness. The thickness of the films of *S. foetida* in combination with carbopol 934 (A1-A6) was measured about 0.266±0.0037, 0.278±0.0033, 0.288±0.0024, 0.312±0.0029, 0.300±0.0027 and 0.316±0.0033 mm respectively. The thickness of the film prepared with *S. foetida* alone (A7) was measured about 27.66±1.24 mm and the films prepared with carbopol 934P alone (A8) was measured about 0.252±0.0025 mm.

Table 2: Physical evaluation of buccal films

Evaluation parameters	Formulation codes							
	A1	A2	A3	A4	A5	A6	A7	A8
Weight variation (mg)	29.13±1.17	30.90±1.31	31.46±1.13	32.20±1.17	33.26±1.34	33.9±1.14	27.66±1.24	27.23±1.27
Thickness of film (mm)	0.266±0.0037	0.278±0.0033	0.288±0.0024	0.312±0.0029	0.300±0.0027	0.316±0.0033	27.66±1.24	0.252±0.0025
Swelling index (%)	14.90±0.85	19.6±0.55	15.24±1.37	18.96±1.02	20.09±1.02	17.9±1.34	13.98±0.02	18.18±1.3
Surface pH	6.58±0.152	6.62±0.125	6.61±0.115	6.68±0.173	6.64±0.115	6.52±0.150	6.70±0.171	6.72±0.119
PMA (%)	2.93±0.092	2.88±0.09	3.84±0.015	3.88±0.115	2.13±0.120	2.01±0.066	2.27±0.124	3.80±0.011
PML (%)	1.22±0.01	1.02±0.02	1.42±0.01	1.24±0.01	1.98±0.04	1.65±0.03	1.78±0.06	1.31±0.03
Folding endurance	94±1	96±3	102±2	108±1	99±2	95±3	98±1	93±3
Mucoadhesive strength (g)	5±0.40	9±0.47	12±0.40	7±0.30	10±0.34	11±0.37	9±0.27	8±0.42
Drug content uniformity (%)	98.0±1.0	98.90±0.291	99.96±0.057	99.92±0.111	99.16±0.292	99.50±0.50	99.60±0.08	99.90±0.12

PMA: Percentage moisture absorption, PML: Percentage moisture loss

The average swelling index of all films given is in Table 2. The drug loaded films were tested for uniformity of swelling index. The swelling index of the films of *S. foetida* in combination with carbopol 934 (A1-A6) was found to be 14.90±0.85%, 19.6±0.55%, 15.24±1.37%, 18.96±1.02%, 20.09±1.02% and 17.9±1.34% respectively. The average swelling index of films prepared with *S. foetida* alone (A7) was found to be 13.98±0.02% whereas the film prepared with carbopol 934 alone (A8) was found to be 18.18±1.3% respectively. All the films prepared with SFG alone, carbopol 934P alone and in combination showed adequate swelling behavior. The % swelling shown by all these films may confirm their bioadhesive behavior because too much swelling of the polymer lack the bioadhesive property.

The surface pH of all films is given in Table 2. The surface pH of the films prepared with *S. foetida* in combination with carbopol 934P (A1-A6) was found to be 6.58±0.152, 6.62±0.125, 6.61±0.115, 6.68±0.173, 6.64±0.115 and 6.52±0.150 pH respectively. The average pH of the films prepared with *S. foetida* alone (A7) was found to be 6.70±0171 and the film prepared with carbopol 934P alone (A8) was found to be 6.72±0.119. The standard deviation values calculated for all the films are very low which conclude that the surface pH of all the films was uniform and within the range. Considering the fact that acidic or alkaline pH may cause irritation to the buccal mucosa and influence the degree of hydration of polymer, the surface pH of the buccal films was determined to optimize both drug permeation and mucoadhesion. Attempts were made to keep the surface pH as close to buccal/salivary pH as possible for developing the buccal films. The surface pH of all the films is within the range of salivary pH. No significant difference was found in surface pH of prepared films.

The % moisture absorption of the films prepared with *S. foetida* in combination with carbopol 934P (A1-A6) was found to be 2.93±0.092, 2.88±0.09, 3.84±0.015, 3.88±0.115, 2.13±0.120 and 2.01±0.066 % respectively. The average % moisture absorbance of the films prepared with *S. foetida* alone (A7) was found to be 2.27±0.124 % and the films prepared with carbopol 934P alone (A8) was found to be 3.80±0.011%.

The % moisture loss of the films prepared with *S. foetida* in combination with carbopol 934P (A1-A6) was found to be 1.22±0.01, 1.02±0.02, 1.42±0.01, 1.24±0.01, 1.98±0.04 and 1.65±0.03 % respectively. The average % moisture loss of the films prepared with *S. foetida* alone (A7) was found to be 1.78±0.06 % and the films prepared with carbopol 934P alone (A8) was found to be 1.31±0.03%.

The folding endurance of films focuses on the flexible nature of films. The folding endurance of the films is given in Table 2. The drug loaded films were studied for folding endurance. The folding endurances of the films of *S. foetida* in combination with carbopol 934P (A1-A6) was found to be 94±1, 96±3, 102±2, 108±1, 99±2 and 95±3 whereas the folding endurance of films prepared with *S. foetida* alone (A7) was found to be 98±1 respectively and the films prepared with carbopol 934P alone (A8) was found to be 93±3. The folding endurance of all the films was found to be optimum which imparted good physical and mechanical strength to the films.

The mucoadhesive strength of the films prepared with *S. foetida* in combination with carbopol 934P (A1-A6) was found to be 5±0.40, 9±0.47, 12±0.40, 7±0.30, 10±0.34 and 11±0.37 g respectively. The mucoadhesive strength of the films prepared with *S. foetida* alone (A7) was found to be 8±0.42 g and the films prepared with carbopol 934P alone (A8) was found to be 9±0.27 g. The mucoadhesive strength exhibited by the films was excellent and adequate for desired adhesion to buccal region.

Ranitidine HCl buccal films were prepared using *S. foetida* as natural polymer and carbopol 934P as synthetic polymer were subjected to the evaluation for uniform dispersion of drug throughout the film. For each study, three films were used, and the average drug content was calculated. The results are shown in Table 14. The drug was dispersed in the range of 98.00-99.96% suggesting that the drug was uniformly dispersed throughout the films. The standard deviation value calculated for such formulation is very less, which suggest that the results are reproducible, and accuracy was maintained in the method used to prepare the films.

The *in-vitro* drug release study was carried out using Franz diffusion cell. The detailed in-vitro release data of all the prepared formulations at the end of 12 hrs are given in Table 2 and Figs. 1 and 2.

In vitro drug release studies were performed for all the prepared formulation using phosphate buffer (pH 6.8) as dissolution medium and measuring drug concentration UV spectrophotometrically at 313 nm. The studies were performed for 12 hrs. The results of *in vitro* studies are shown in the Table. 2. Distinguishable difference was observed in the release of Ranitidine HCl containing SFG and carbopol 934P in comparison with plain SFG and plain carbopol 934P films. The graph was plotted by taking Cumulative percentage release Vs Time and the graphs are shown in the Figs. 2 and 3. The cumulative percentage drug release was observed in the formulation A3 after 12 hrs was found to

Fig. 1: Ranitidine HCl buccal films

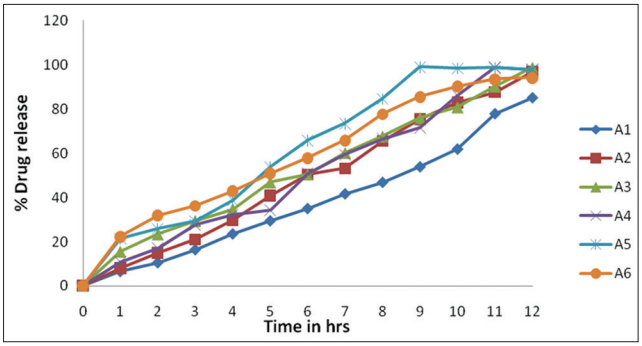

Fig. 2: Cumulative % drug release from formulation A1-A6.

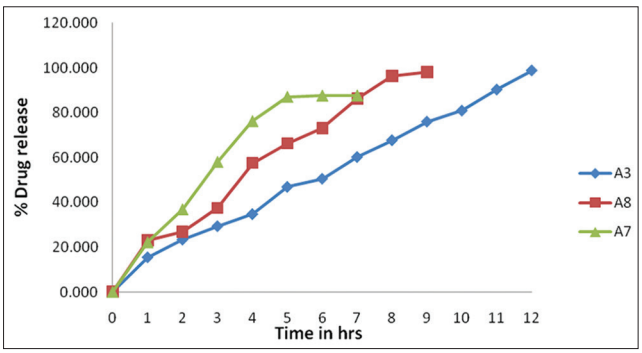

Fig. 3: Cumulative % drug release from formulation A3, A7 and A8.

be 98.79%. The observed results were in the formulation A3 showing good release characteristics due to hydration and excessive swelling of the polymer. So out of all the formulation A3 retard the release rate and used to achieve the sustained release characteristics up to 12 hrs than the other formulations.

The release profiles were subjected to various kinetic equations like Higuchi diffusion equation and Peppas exponential equation. The regression coefficient values of this kinetic equation are very nearer to one suggesting that plots are fairly linear and slope values of the Peppas equation were (>1) suggest that drug was released by diffusion mechanism following non-Fickian transport. Finally, the films from A3 and A4 batches were subjected to stability studies for a period of one month, and they were evaluated for surface appearance and texture, weight variation, thickness and content uniformity. It was seen that there were no as such any changes in the stated parameters.

Finally, mucoadhesive buccal films (A3) were subjected to stability studies which were carried out in order to ascertain the chemical and physical stability of the formulations. No marked changes in the respective properties like physical appearance, weight variation, thickness and drug content of formulations were observed at storage temperature of 25°C and 40°C. The results are shown in Tables 3 and 4.

CONCLUSION

The Ranitidine buccal films were prepared by the method of solvent casting technique employing 'O' shape ring placed on a mercury surface as substrate. It can conclude that buccal films of SFG in combination with carbopol 934P can be prepared for systemic drug delivery. This combination has shown very good physical stability, excellent mucoadhesive strength, good stability and prolonged drug release.

Table 3: Stability studies of buccal film at 25°C

Formulation	A3		
Period (days)	0	15	30
Physical appearance	No change	No change	No change
Weight variation (mg)	34.10±1.13	34.08±1.07	34.06±1.05
Thickness (mm)	0.284±0.0033	0.282±0.0028	0.280±0.0029
Drug content uniformity (%)	98.90±0.291	98.00±0.280	97.54±0.292

Table 4: Stability studies of buccal film at 40°C

Formulation	A3		
Period (days)	0	15	30
Physical appearance	No change	No change	No change
Weight variation (mg)	34.10±1.21	34.10±1.19	34.11±1.21
Thickness (mm)	0.284±0.0033	0.275±0.0028	0.270±0.0022
Drug content uniformity (%)	98.90±0.291	98.50±0.282	98.00±0.292

Thus, these polymers in combination improve the bioavailability of the drug by circumventing hepatic first pass metabolism and have wider prospects to be incorporated in buccal films as mucoadhesive drug delivery system.

ACKNOWLEDGMENT

Authors are thankful to Dr. D. R. Chaple (Principal), J. L. Chaturvedi College of Pharmacy, Nagpur, for their support and encouragement in carrying out this work.

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