



Research Article

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Formulation and evaluation of sodium alginate based Ramipril buccal films

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ABSTRACT

As reported in the literature, Ramipril has poor bioavailability, easily undergoes first pass metabolism. Hence an attempt was made to prepare mucoadhesive buccal films containing Ramipril as model drug. Various films were prepared by employing sodium alginate with different ratios. The prepared films were evaluated for their physical parameters like thickness and size, folding endurance, drug content, bioadhesive strength etc... The drug content of all the formulations was found to be uniform. The ex-vivo diffusion studies were conducted with Franz diffusion cell. The results indicated that the film prepared with 650 and 325mg of sodium alginate showed sustained drug release. To these two formulations 30% of the plasticizer was added. Only F2 and F9 showed significant drug release. Films having 50% of plasticizer and permeation enhancer showed fast drug release at the end of 7 and 10hrs. IR studies showed no interaction between drug and polymer. Dissolution studies were conducted for all the formulations only F3 formulation showed 90% of drug release in 7hrs.

Key words: Ramipril, sodium alginate, bioadhesion, Franz diffusion cell.

INTRODUCTION

In the current scenario the research in the area of formulating the drugs acting on the cardiovascular system is increasing as the existing formulations with the older drugs and the formulations with newly approved drugs are showing a lot of disadvantages like delayed and short term drug release[1,2]. To overcome this problem the development of buccal films is considered to be one of the greater milestones. Buccal route offers various advantages in systemic delivery of drugs when compared to oral route by avoiding first pass metabolism and also useful for localized delivery of the drugs[3,4]. The oral cavity is easily accessible for self medication and hence it is well accepted by patient, and it is safe since the device can be easily administered and even removed from the site of application, stopping the input of drug whenever desired.[4,5]

Ramipril was selected as model drug because it has all the pharmacokinetics and physico-chemical properties required for controlled release and has oral bioavailability of 28%. The present study is an attempt to formulate buccal dosage form of ramipril namely films using different polymers and an adjuvant therapy to avoid hepatic first pass metabolism.[6,7]

EXPERIMENTAL SECTION

Materials : Ramipril was a gift sample from Aurobindo Pharma Ltd, Hyderabad. Sodium alginate was purchased from SD Fine Chemicals Mumbai, propylene glycol and glycerol were procured from Merck Specialties Ltd.

Methods :**Performulation studies:**

FTIR studies: to investigate any possible interaction between the drug and the utilized polymers under investigation FT-IR spectrophotometer method was used. The IR spectra of pure drug and its physical mixture were carried out by using FT-IR spectrophotometer. [8]

Preparation of buccal films: the buccal films of ramipril were prepared by using various polymers and in combination with PVP as seen in table 1. The films are prepared by solvent casting technique using film forming mucoadhesive polymers. [9,10] Accurately weighed sodium alginate was dissolved in 10ml of water. The beaker containing the polymer and water was kept aside for 5 min for swelling of polymer and this solution was kept under continuous magnetic stirring. Simultaneously ramipril was accurately weighed in quantity such that 1cm² film containing 20mg and dissolved in 10ml water in separate beaker, then drug solution was added to the polymer solution and was mixed thoroughly with the help of magnetic stirrer.[11,12] Then % of propylene glycol and glycerol was added to the above mixture. After uniform mixing the entire mixture was sonicated to remove the bubbles. The solution was then poured in a petri plate and film formed is dried, stored in desiccator.

Table 1: formulation of buccal films

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Ramipril	597	597	597	597	597	597	597	597	597	597	597	597	597
Sodium alginate	300	325	350	400	450	500	550	600	650	-	-	-	-
Propylene glycol	97.5	105	113	120	150	165	180	187.5	195	121	165	104	114
Glycerol	97.5	105	113	120	150	165	180	187.5	195	176	158	143	118
Water (ml)	10	10	15	20	20	20	20	20	20	-	10	-	20
PVP K90	-	-	-	-	-	-	-	-	-	600	-	1200	-
Ethanol (ml)	-	-	-	-	-	-	-	-	-	10	-	20	-
Pectin	-	-	-	-	-	-	-	-	-	-	600	-	120

Evaluation tests:

1. Physical appearance: the films were observed visually for their physical appearance such as color and transparency.
2. Surface texture: the surface texture was evaluated by pressing the film.
3. Thickness and size: four films of each formulation were taken and the thickness of the film was measured using screw gauge at different places.
4. Folding endurance : The folding endurance was measured manually. A small strip of film of each formulation was taken and folded at the same place till it breaks. The number of times a film could be folded at the same place gave the value of folding endurance. Average of three determinations were calculated and standard deviation were computed.[13]
5. The surface pH: The surface pH of the film was determined by allowing the film to swell by keeping them in contact with 0.5ml of distilled water for 1hr in 50ml glass beaker. The surface pH was noted by bringing a combined glass electrode near the surface of the film for 1min using pH meter. The pH was recorded and average of three determination and SD was computed.[14]
6. Drug content: Drug content uniformity was determined by tacking film area of 1.5cm² from each formulation and it was placed in 50ml of volumetric flask contained 50ml of phosphate buffer of pH6.6. It was kept aside for 6hrs and volume was made up to 100ml with the buffer of pH 6.6.
7. Percent moisture absorption: The percent moisture absorption test was carried out to check the physical stability of the buccal films at high humid conditions. In the percent study the moisture absorption capacity of the films were determined as follows. Three 1 cm 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 dessicator at 79.5%. after 3 days the films were removed, weighed and Percent moisture absorption calculated. [15]

8. Percent moisture loss: It was done to check the integrity of films at dry conditions. Three 1 cm diameter films was cut out and weighed accurately and kept in desiccators containing fused anhydrous calcium chloride. After 72hrs the films were removed, weighed. Average percent moisture loss of three films was found out.[16]

9. Water vapor transmission rate: For water vapor transmission rate 13 study vials of equal diameter were used as transmission cells. These cells were washed thoroughly and dried in an oven. About 1gm of calcium chloride was taken in the cell and the polymeric films measuring 2 cm² areas were fixed over the brim with the help of 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 72hrs. from increase in weights the amount of water vapor transmitted and the rate at which water vapor transmitted were calculated.

10. Swelling index studies: Buccal films of 2cm² area from each formulation were taken accurately weighed by using single pan balance and it was placed in a petridish containing 50ml distilled water. After different time interval 5min, 10min, and 20min film was removed and blotted with filter paper and weighed again. The weight of the film was noted and swelling index was calculated.[17]

11. In vitro bioadhesion test: A double pan physical balance was taken and both the pans were removed. The left pan was replaced with a brass wire the right pan was replaced with a lighter pan. In the left pan propylene block was placed. The goat cheek pouch was carefully excised without removing connective and adipose tissue and stored in saline solution. The left side pan was placed in the beaker containing phosphate buffer of pH 6.6 and kept at 37⁰ C. The film was taken and attached to upper propylene cylinder and goat cheek pouch was attached on the lower propylene block. A preload weight of 30gm was placed on the left pan of the balance for 10min. the weights were then removed slowly and weights were added slowly in increasing order to the right pan till the patch separates from the mucosal surface. The weights required for complete detachment of film from mucosal surface was noted. Average of three determinations was calculated.[18]

12. In vitro release studies: The drug release studies were performed with USP dissolution test apparatus using paddle at 50rpm. Each film was fixed on a glass slide with the help of cyanoacrylate adhesive so that drug could be release only from upper face. Then the slide has immersed in the vessel containing 500ml of pH 6.8 phosphate buffer solution. The aliquots of 1ml 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. Samples were analyzed at 210nm.

13. In situ studies: In situ release studies were carried out for the selected formulation by using goat cheek pouch membrane. In this method goat cheek pouch was attached to one end of donor compartment of area 1.5cm² was selected and the above procedure was repeated.

14. Ex vivo permeation studies of mucoadhesive buccal films of ramipril through an excised layer of goat buccal mucosa washed in isotonic phosphate buffer pH 6.8 were carried out by using modified franz diffusion cell. A 2cm diameter film of each formulation under study was placed in intimate contact with the excised goat buccal mucosa and the top side was covered with aluminium foil as a backing membrane. The contents of receptor compartment filled with 30ml of pH 6.8 phosphate buffer were stirred and samples were withdrawn at every one hour, filtered, diluted suitably and then analyzed using U.V. Spectrophotometer at 210nm.

15. SEM (scanning electron microscope): The morphology of the selected film (F1) was characterized before and after diffusion study, drug distribution ability and undiffused drug was monitored in the study.

RESULTS AND DISCUSSION

Mucoadhesive strength was conducted only for the formulation F9, as the percent release of the drug is better when compared with the other formulations. This has shown better bioadhesive strength because of higher sodium alginate. All the prepared formulations of Ramipril buccal film has shown pH range within the range of salivary. Among all the formulations the high value of PMA can be observed in F8 and F9 this is due to the increased swelling behavior of sodium alginate and PML value was due to the high degree of hydration of mucoadhesive polymer like sodium alginate. The drug loaded films were showing more swelling percentage than the drug free films this is due to increase water up take of the drug. The swelling was more in formulation F8 and F9 which contain high amount of sodium alginate. Water vapor transmission studies indicate that all films were permeable to water vapour. The folding endurance was increased with the addition of sodium alginate. The observed results of content uniformity indicated that the drug was uniformly dispersed.

Table 2 : Preformulation studies of Ramipril

Formulation code	Average weight	Folding endurance	Surface pH	PMA	PML	Swelling index	WVT	Thickness	Drug content
F1	225.11	488	6.5	2.84	1.42	69.90	6.02	88.09	98.09
F2	290.05	522	6.4	3.88	1.24	69.6	12.6	140.9	98.29
F3	225.16	508	6.2	2.93	0.96	78.24	78.24	88.21	98.84
F4	225.21	105	6.5	2.95	1.06	87.96	87.96	87.99	98.57
F5	290.28	128	6.2	4.07	1.16	131.2	131.2	141.1	98.06
F6	220.17	115	6.1	3.29	1.09	135.4	19.2	88.41	98.07
F7	224.58	458	6.2	2.08	1.35	141.2	22	90.13	98.27
F8	290.28	457	6.3	4.92	1.42	144.5	23.04	141.1	98.43
F9	224.59	464	6.1	4.35	0.73	153.3	25.01	89.9	98.28

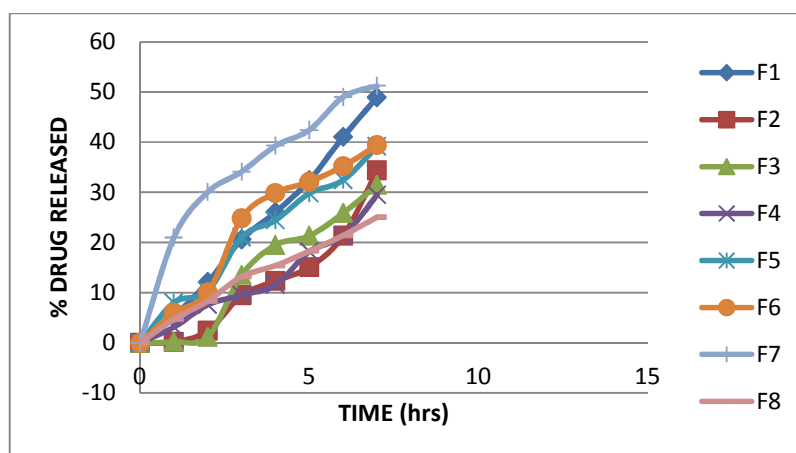


Fig 1: In vitro drug release studies

Fig 2: ex-vivo studies of buccal formulations

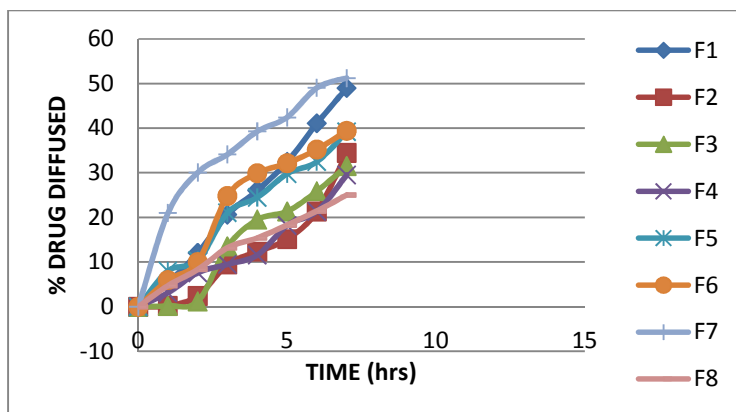
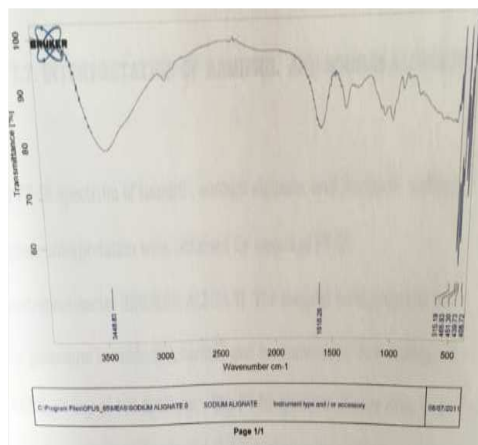
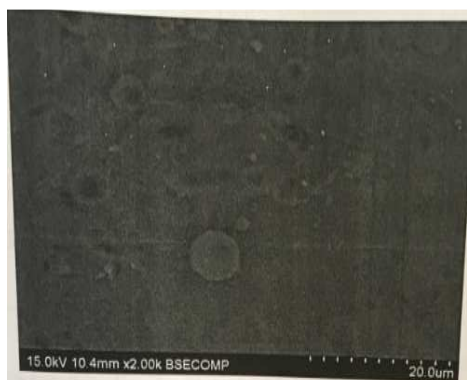
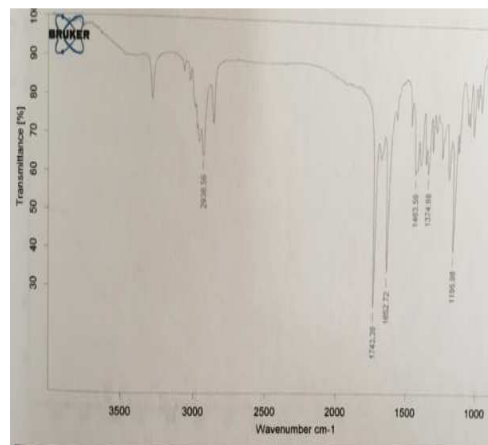


FIG 3: SEM photographs of buccal film



FTIR spectrum of formulation



FTIR spectrum of pure drug

The FTIR spectrum of pure drug and sodium alginate are shown in the above figure, as observed no interaction was found between the drug and polymer. SEM photos have clearly indicated that the drug was uniformly distributed and released from the selected formulation. The cumulative percentage drug release was observed in the formulation F7 was seen to achieve the controlled release characteristics more than 7hrs than other formulations.

CONCLUSION

Among the various routes of administration for novel drug delivery systems, buccal route of drug administration may be promising approach to overcome the problems such as hepatic first pass metabolism, reduction of bioavailability, frequent dosing. The selected drug ramipril is widely used as a cardiovascular for treatment of hypertension, congestive cardiac failure and kidney failure. Secondly it undergoes hepatic first pass metabolism thus bioavailability is reduced to 40% only. It has also been reported to cause gastrointestinal discomfort. Hence buccal films of ramipril were prepared using polymer sodium alginate in combination with propylene glycol and glycerol by solvent casting technique. The formulations prepared were uniform in weight, thickness and drug content, surface pH values were found to be compatible with buccal surface. The drug release studies showed prolonged release for 7 hrs. Hence buccal patches of ramipril can prove to be best alternate to already existing conventional therapy.

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